US009181298B2

(12) **United States Patent**
Marsault et al.

(10) **Patent No.: US 9,181,298 B2**
(45) **Date of Patent: *Nov. 10, 2015**

(54) **INTERMEDIATES FOR MACROCYCLIC COMPOUNDS**

(75) Inventors: **Eric Marsault**, Sherbrooke (CA); **Kamel Benakli**, Blue Bell, PA (US); **Hamid Hoveyda**, Brussels (BE); **Mark Peterson**, Sherbrooke (CA); **Sylvie Beaubien**, Sherbrooke (CA); **Luc Oullet**, Sherbrooke (CA); **Carl St-Louis**, Sherbrooke (CA); **Sophie Beauchemin**, Sherbrooke (CA)

(73) Assignee: **OCERA THERAPEUTICS, INC.**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1247 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/273,638**

(22) Filed: **Nov. 19, 2008**

(65) **Prior Publication Data**

US 2009/0240027 A1 Sep. 24, 2009

Related U.S. Application Data

(63) Continuation of application No. 10/872,142, filed on Jun. 18, 2004, now Pat. No. 7,521,420.

(60) Provisional application No. 60/479,223, filed on Jun. 18, 2003.

(30) **Foreign Application Priority Data**

Jun. 18, 2004 (WO) PCT/CA04/00913

(51) **Int. Cl.**

C07C 49/84	(2006.01)
C07C 45/46	(2006.01)
A61K 31/122	(2006.01)
C07K 5/08	(2006.01)
A61K 38/12	(2006.01)
A61K 38/22	(2006.01)
C07D 273/00	(2006.01)
C07D 413/06	(2006.01)
C07D 498/04	(2006.01)
C07K 5/087	(2006.01)
C07K 5/097	(2006.01)

(52) **U.S. Cl.**

CPC ***C07K 5/0827*** (2013.01); ***A61K 38/12*** (2013.01); ***A61K 38/2214*** (2013.01); ***C07D 273/00*** (2013.01); ***C07D 413/06*** (2013.01); ***C07D 498/04*** (2013.01); ***C07K 5/0812*** (2013.01); ***C07K 5/0821*** (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/519; A61K 49/10; A61K 38/12; A61K 31/54; A61K 31/341; C07D 401/12; C07D 405/06; C07D 407/12; C07D 413/12; C07D 265/32

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,920,102	A	4/1990	Gidda et al.
4,997,820	A	3/1991	Sutter et al.
5,008,249	A	4/1991	Omura et al.
5,143,915	A	9/1992	Rovnyak et al.
5,175,150	A	12/1992	Omura et al.
5,179,087	A	1/1993	Donald et al.
5,196,452	A	3/1993	Hwang et al.
5,252,579	A	10/1993	Skotnicki et al.
5,292,741	A	3/1994	Delaszlo et al.
5,376,663	A	12/1994	Cooper et al.
5,380,888	A	1/1995	Sum et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EP	0818431	1/1998
EP	0852232 A1	7/1998

(Continued)

OTHER PUBLICATIONS

U.S. Appl. No. 13/173,929, Fraser et al.*

Uenaka et al., Bulletin of the Chemical Society of Japan, 1936, 11, 19-26.*

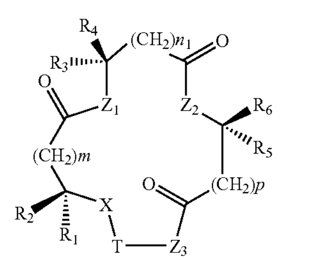
Hubert, J. Chem. Soc., 1963, 4088-4091.*

(Continued)

Primary Examiner — Marcela M Cordero Garcia
Assistant Examiner — Kaipeen Yang
(74) *Attorney, Agent, or Firm* — Myers Bigel Sibley & Sajovec, P.A.

(57) **ABSTRACT**

The present invention is directed to novel macrocyclic compounds of formula (I) and their pharmaceutically acceptable salts, hydrates or solvates:



(I)

wherein R_1, R_2, R_3, R_4, R_5, R_6, n_1, m, p Z_1, Z_2, and Z_3 are as describe in the specification. The invention also relates to compounds of formula (I) which are antagonists of the motilin receptor and are useful in the treatment of disorders associated with this receptor and with or with motility dysfunction.

3 Claims, 21 Drawing Sheets

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,418,224 A 5/1995 Hoeltje et al.
5,422,341 A 6/1995 Macielag et al.
5,426,103 A 6/1995 Macpherson et al.
5,432,261 A 7/1995 Kurono et al.
5,457,111 A 10/1995 Luly et al.
5,457,194 A 10/1995 Luly et al.
5,459,049 A 10/1995 Kurono et al.
5,470,830 A 11/1995 Macielag et al.
5,470,961 A 11/1995 Harada et al.
5,523,401 A 6/1996 Freiberg et al.
5,530,119 A 6/1996 Kawai et al.
5,530,120 A 6/1996 Luly et al.
5,534,632 A 7/1996 Or et al.
5,538,961 A 7/1996 Freiberg et al.
5,554,605 A 9/1996 Freiberg et al.
5,561,137 A 10/1996 Or et al.
5,561,139 A 10/1996 Luly et al.
5,561,140 A 10/1996 Kawai et al.
5,561,228 A 10/1996 Or et al.
5,563,172 A 10/1996 Wagner et al.
5,599,927 A 2/1997 Or et al.
5,604,234 A 2/1997 Or et al.
5,604,294 A 2/1997 Luly et al.
5,612,350 A 3/1997 Or et al.
5,624,949 A 4/1997 Heath, Jr. et al.
5,643,918 A 7/1997 Wagner et al.
5,658,888 A 8/1997 Koga et al.
5,696,108 A 12/1997 Heath, Jr. et al.
5,698,578 A 12/1997 Heath, Jr. et al.
5,708,002 A 1/1998 Luly et al.
5,710,145 A 1/1998 Engel et al.
5,712,253 A 1/1998 Lartey et al.
5,719,175 A 2/1998 Heath, Jr. et al.
5,731,320 A 3/1998 Wagner et al.
5,734,012 A 3/1998 Dharanipragada et al.
5,811,515 A 9/1998 Grubbs et al.
5,817,807 A 10/1998 Bridger et al.
5,849,691 A 12/1998 Majer et al.
5,854,407 A 12/1998 Harada et al.
5,888,971 A 3/1999 Greco et al.
5,912,235 A 6/1999 Hoeltje et al.
5,952,320 A 9/1999 Davidsen et al.
5,969,132 A 10/1999 Farr et al.
5,972,939 A 10/1999 Chen et al.
6,043,357 A 3/2000 Abbenante et al.
6,080,838 A 6/2000 Etzkorn et al.
6,100,239 A 8/2000 Ataka et al.
6,100,377 A 8/2000 Greene
6,121,257 A 9/2000 Kawai et al.
6,124,453 A 9/2000 Fehr et al.
6,165,985 A 12/2000 Jasserand et al.
6,228,986 B1 5/2001 Lanter et al.
6,255,285 B1 7/2001 Kotake et al.
6,281,352 B1 8/2001 Xue et al.
6,307,044 B1 10/2001 Dorow et al.
6,329,376 B1 12/2001 Bergman
6,348,447 B1 2/2002 Hellstrom et al.
6,350,755 B1 2/2002 Desolms et al.
6,358,985 B1 3/2002 Anthony et al.
6,380,228 B1 4/2002 Stump et al.
6,384,031 B2 5/2002 Chen et al.
6,392,040 B2 5/2002 Chen et al.
6,403,775 B1 6/2002 McDaniel
6,410,534 B1 6/2002 Dinsmore et al.
6,413,964 B1 7/2002 Desolms et al.
6,423,714 B2 7/2002 Chen et al.
6,441,017 B1 8/2002 Bell et al.
6,511,980 B2 1/2003 Johnson et al.
6,534,506 B2 3/2003 Nguyen et al.
6,548,501 B2 4/2003 Hakkinen
6,562,823 B1 5/2003 Dinsmore et al.
6,562,963 B2 5/2003 Dorow et al.
6,566,385 B2 5/2003 Desolms et al.
6,586,630 B1 7/2003 Matsuoka et al.
6,608,027 B1 8/2003 Tsantrizos et al.
6,610,722 B2 8/2003 Stump et al.
6,624,165 B2 9/2003 Chen et al.
6,632,818 B2 10/2003 Dinsmore
6,653,334 B1 11/2003 Yamazaki et al.
6,660,832 B1 12/2003 Jefferson et al.
6,667,309 B2 12/2003 Chen et al.
6,720,433 B2 4/2004 Matsuoka et al.
7,109,226 B2 9/2006 Yamazaki et al.
7,169,899 B1 * 1/2007 Deslongchamps et al. ... 530/371
7,452,862 B2 * 11/2008 Deslongchamps et al. 514/1.1
7,476,653 B2 * 1/2009 Hoveyda et al. 514/1.1
7,491,695 B2 * 2/2009 Fraser et al. 514/1.1
7,521,420 B2 * 4/2009 Fraser et al. 514/1.1
7,550,431 B2 * 6/2009 Deslongchamps et al. 514/1.1
7,553,969 B1 6/2009 Matsuoka et al.
8,008,440 B2 * 8/2011 Deslongchamps et al. ... 530/371
2001/0041701 A1 11/2001 Chen
2002/0002192 A1 1/2002 Chen
2002/0013352 A1 1/2002 Johnson et al.
2002/0016294 A1 2/2002 Venkatraman
2002/0049217 A1 4/2002 Desolms et al.
2002/0056106 A1 5/2002 Takahashi et al.
2002/0058286 A1 5/2002 Danishefsky et al.
2002/0058817 A1 5/2002 Danishefsky et al.
2002/0091151 A1 7/2002 Danishefsky et al.
2002/0103238 A1 8/2002 Chen
2002/0111484 A1 8/2002 Chen
2002/0192773 A1 12/2002 Walsh et al.
2003/0158377 A1 8/2003 Walsh et al.
2003/0176643 A1 9/2003 Matsuoka et al.
2003/0181363 A1 9/2003 Llinas-Brunet
2003/0191053 A1 10/2003 Matsuoka et al.
2003/0203906 A1 10/2003 Johnson et al.
2003/0211982 A1 11/2003 Saragovi et al.
2003/0224977 A1 12/2003 Llinas-Bruunet et al.
2003/0236199 A1 12/2003 Pulley et al.
2003/0236240 A1 12/2003 Pulley et al.
2004/0002448 A1 1/2004 Tsantrizos et al.
2004/0038872 A1 2/2004 Campbell et al.
2004/0063640 A1 4/2004 Burg et al.
2005/0049234 A1 3/2005 Deslongchamps et al.
2005/0119169 A1 6/2005 Deslongchamps et al.
2005/0137127 A1 6/2005 Deslongchamps et al.
2008/0194672 A1 * 8/2008 Hoveyda et al. 514/450
2008/0287371 A1 * 11/2008 Fraser et al. 514/18
2009/0137835 A1 5/2009 Marsault et al.
2009/0170757 A1 * 7/2009 Fraser et al. 514/11
2009/0221689 A1 9/2009 Marsault et al.
2009/0275648 A1 * 11/2009 Fraser et al. 514/454
2009/0312540 A1 * 12/2009 Deslongchamps et al. ... 540/455
2010/0093720 A1 * 4/2010 Marsault et al. 514/234.2
2011/0105389 A1 * 5/2011 Hoveyda et al. 514/4.8
2011/0237785 A1 9/2011 Marsault et al.
2011/0245159 A1 10/2011 Hoveyda et al.

FOREIGN PATENT DOCUMENTS

EP 1116726 A1 7/2001
EP 1174438 A1 1/2002
JP 11001492 A 1/1999
JP 2000044595 A 2/2000
JP 2000256397 A 9/2000
WO WO-95/21186 8/1995
WO WO 97/32594 A1 9/1997
WO WO-98/46631 10/1998
WO WO-98/51665 11/1998
WO WO-00/17231 3/2000
WO WO 00/17231 A1 3/2000
WO WO 0018790 A1 4/2000
WO WO-00/44770 8/2000
WO WO 00/44770 A1 8/2000
WO WO-01/05811 1/2001
WO WO-01/14346 3/2001
WO WO-01/16162 3/2001
WO WO-0125257 4/2001
WO WO 0125257 A2 * 4/2001
WO WO-01/42228 6/2001
WO WO-01/53331 7/2001
WO WO 01/77113 10/2001

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

WO	WO-01/81325	11/2001
WO	WO-02/16369	2/2002
WO	WO-0220510	3/2002
WO	WO-02/40463	5/2002
WO	WO-02/051413	7/2002
WO	WO-02/064623	8/2002
WO	WO-02/070547	9/2002
WO	WO-02/092592	11/2002
WO	WO-03/024996	3/2003
WO	WO 03/053349	7/2003
WO	WO-03/054000	7/2003
WO	WO-03/064455	7/2003
WO	WO-03/068168	8/2003
WO	WO-03/076424	9/2003
WO	WO-03/106480	12/2003
WO	WO-04/00742	12/2003
WO	WO-03102400	12/2003
WO	WO-2004/007483	1/2004
WO	WO-2004/012816	2/2004
WO	WO-2004/018503	3/2004
WO	WO-2004/026881	4/2004

OTHER PUBLICATIONS

Halab et al. "Design, Synthesis, and Conformational Analysis of Azacycloalkane Amino Acids as Conformationally Constrained Probes for Mimicry of Peptide Secondary Structures", *Biopolymers* (*Peptide Science*) 55(2):101-122 (2000).

Partial European Search Report corresponding to European Patent Application No. 10001568.4.

Extended European Search Report corresponding to European Patent Application No. 10001568.4 dated Oct. 22, 2010.

U.S. Appl. No. 12/273,648, filed Nov. 19, 2008, Marsault et al.

Vippagunta et al. Adv. Drug Delivery Ref. (2001) 48, pp. 3-26.

Japanese Office Action corresponding to Japanese Application No. 2006-515603 mailed Apr. 2, 2010.

Hadfield et al. "Dimethanesulphonate esters in receptor mapping studies. 2. Antitumour activities of alkyl and alkoxy dimethanesulphonates substituted on a benzene nucleus.", *Anticancer Drug Des*. 7(3):263-75 (1992) Abstract Only.

U.S. Appl. No. 12/351,395, Marsault et al., filed Jan. 9, 2009.

O'Leary et al. "Preferred Conformation of C-Glycosides. 13. A Comparison of the Conformational Behavior of Several C-, N-, and O-Furanosides", *J. Org. Chem*. 59(22):6629-6636 (1994).

* cited by examiner

General Synthetic Strategy to Conformationally-Defined Macrocycles of the Present Invention

Scheme 1

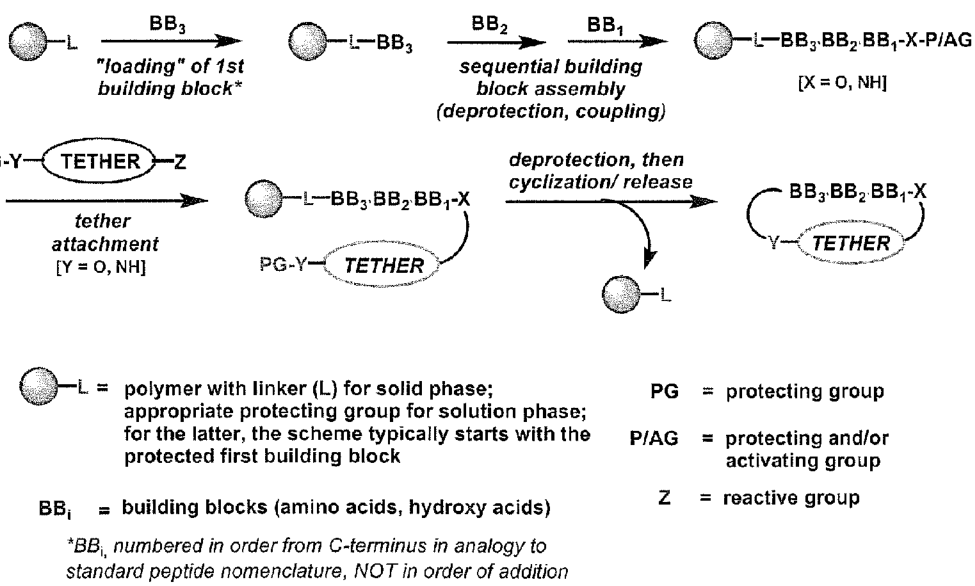
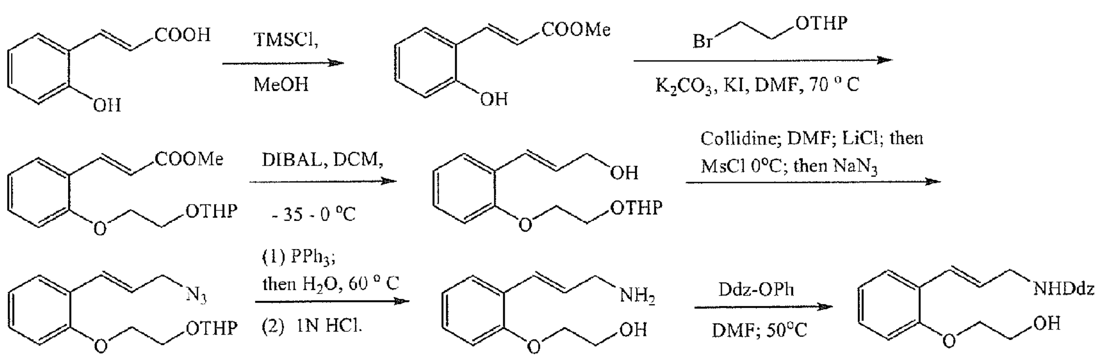


FIG. 1

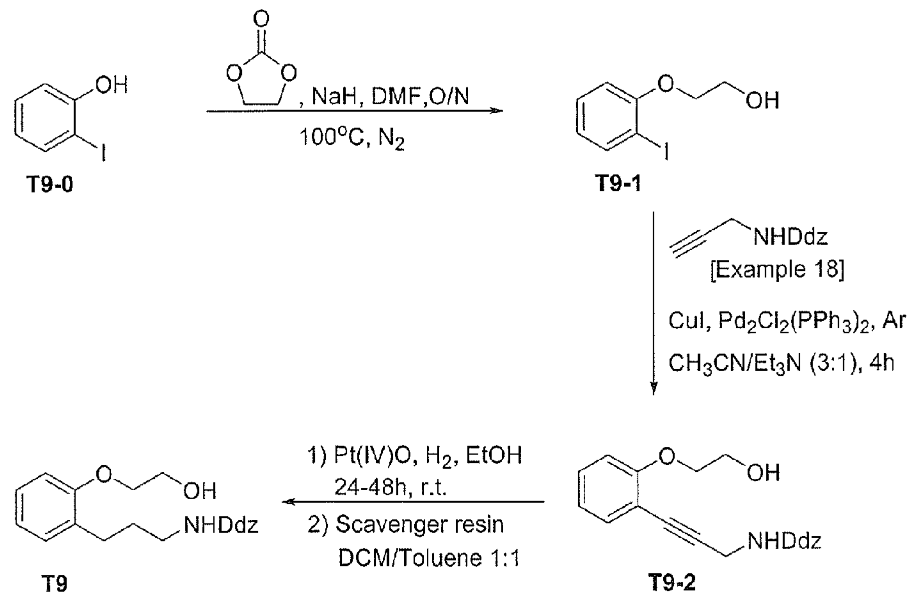
Standard Procedure for the Synthesis of Tether T8



(T8)

FIG. 2

Standard Procedure for the Synthesis of Tether T9



The yield of **Ddz-T9** from **T9-0** on a 65 g scale was 60.9 g (91%)

^{1}H NMR ($CDCl_3$): δ 7.19-7.01, (m, 2H), 6.92-9.83 (m, 2H), 6.53 (bs, 2H), 6.34 (t, 1H), 5.17 (bt, 1H), 4.08 (m, 2H), 3.98 (m, 2H), 3.79 (s, 6H), 3.01 (bq, 2H), 2.66 (t, 3H), 1.26 (bs, 8H);

^{13}C NMR ($CDCl_3$) δ 160.9, 156.8, 155.6, 149.6, 130.4, 127.5, 121.2, 111.7, 103.2, 98.4, 80., 69.7, 61.6, 55.5, 40.3, 30.5, 29.3, 27.4

FIG. 3

Standard Procedure for the Synthesis of Ddz-propargylamine

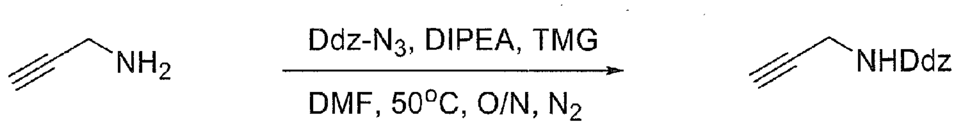
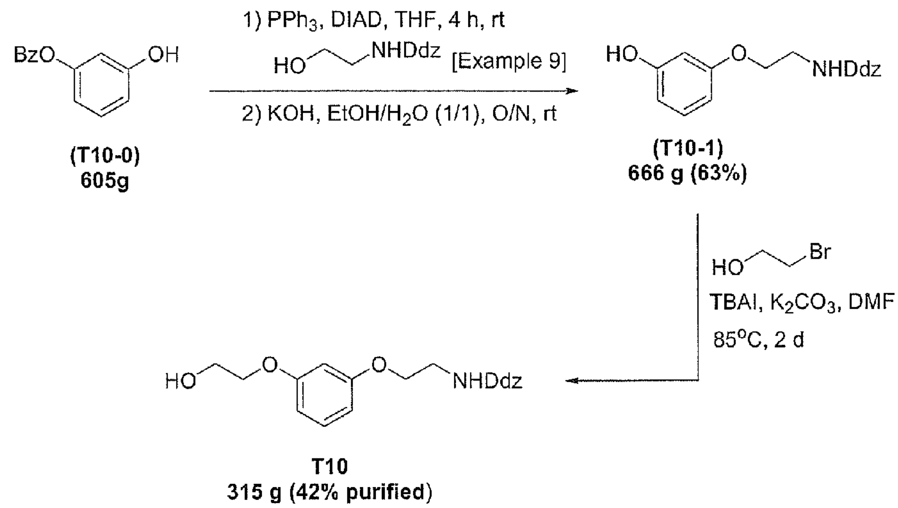


FIG. 4

Standard Procedure for the Synthesis of Tether T10

Method A



TLC (EtOAc/Hexanes 1:1, detection: UV, ninhydrin; R_f = 0.17)

^{1}H NMR ($CDCl_3$) δ 7.18, t, 1H,J = 8.2Hz; 6.51, m, 5H; 6.34, t, 1H, J = 2.2Hz; 5.19, s, 1H; 4.05, t, 2H, J = 5.0Hz; 3.94, m, 4H; 3.75, s, 6H; 3.49, d, 2H J = 5.2Hz; 1.73, s, 6H.

^{13}C NMR ($CDCl_3$) δ 160.856; δ 160.152; 160.005; 155.410; 149.305; 130.279; 107.438; 107.310; 103.163; 101.877; 98.517; 69.488; 67.382; 61.595; 55.427; 40.420; 29.427.

HPLC (standard gradient) t_R: 7.25 min

MS: 420 (M+H)

FIG. 5A

Method B

The second synthetic route to **T10** is presented in the accompanying scheme.

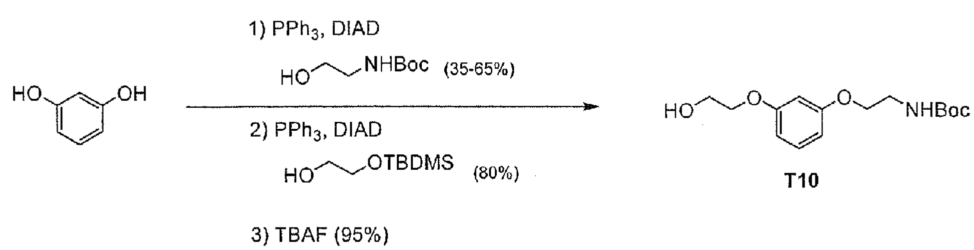
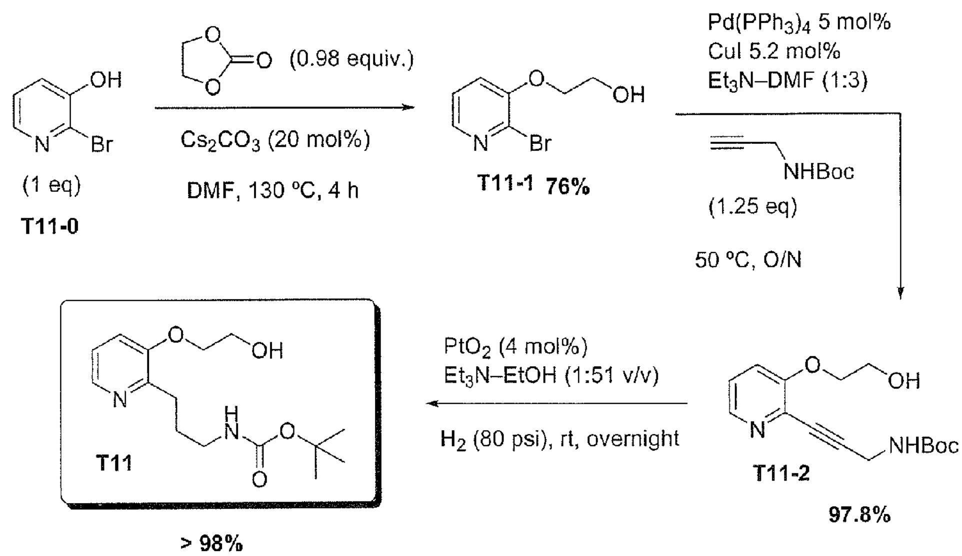


FIG. 5B

Standard Procedure for the Synthesis of Tether T11



TLC (15:85 THF/DCM; detection: UV; R_f: 0.33).

^{1}H NMR (DMSO-d_6) δ 8.00, d, 1H; 7.32, d, 1H; 7.15, m, 1H; 6.44, s, 2H; 6.33, s, 1H; 3.99, t, 2H; 3.71, m, 8H; 2.89, m = 4, 2H; 2.71, t, 2H; 1.71, m = 5, 2H; 1.61, s, 6H.

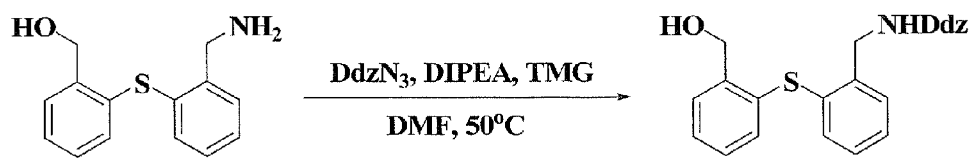
^{13}C NMR, solvent DMSO-d_6) δ 160.879; 153.275; 151.405; 150.447; 140.773; 122.666; 118.934; 103.347; 98.456; 79.778; 70.449; 60.212; 55.717; 55.599; 29.740; 28.592.

HPLC (standard gradient) t_R: 5.4 min

MS: 419 (M+H)

FIG. 6

Standard Procedure for the Synthesis of Tether T12

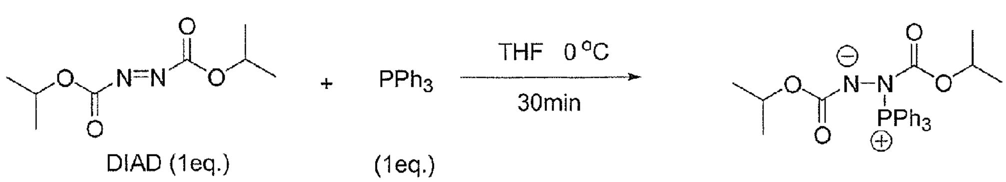


(12-0)

Ddz-T12

FIG. 7

Procedure for Synthesis of PPh_3-DIAD Adduct



Adduct

FIG. 8

Standard Procedure for Attachment of Tethers via Reductive Amination

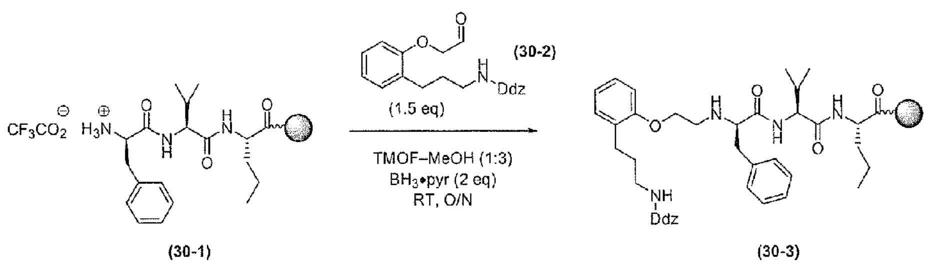


FIG. 9

Standard Procedure for the Synthesis of Tether T28

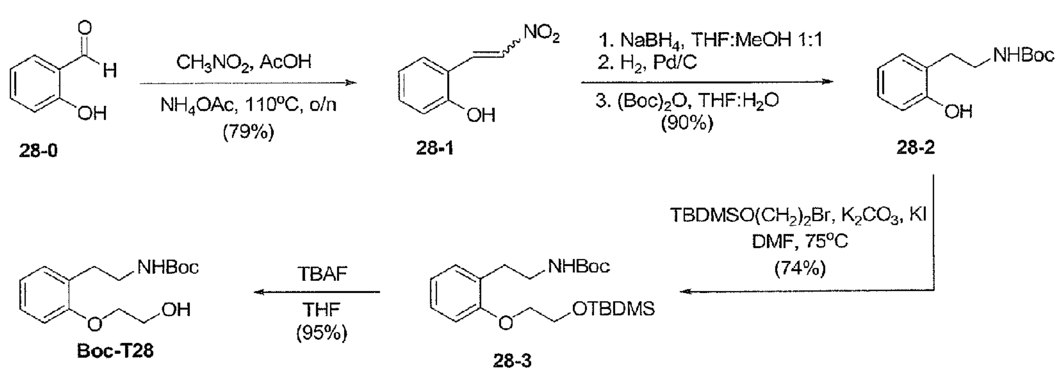
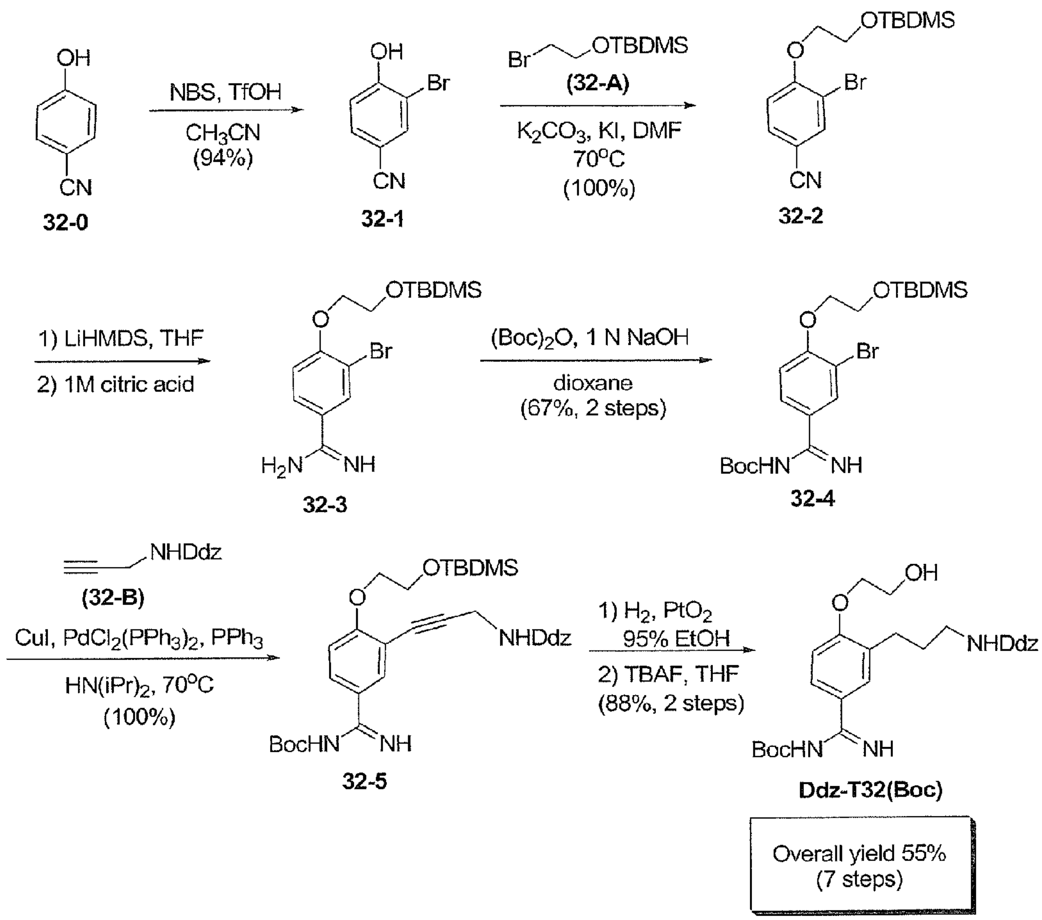


FIG. 10

Standard Procedure for the Synthesis of Tether T32



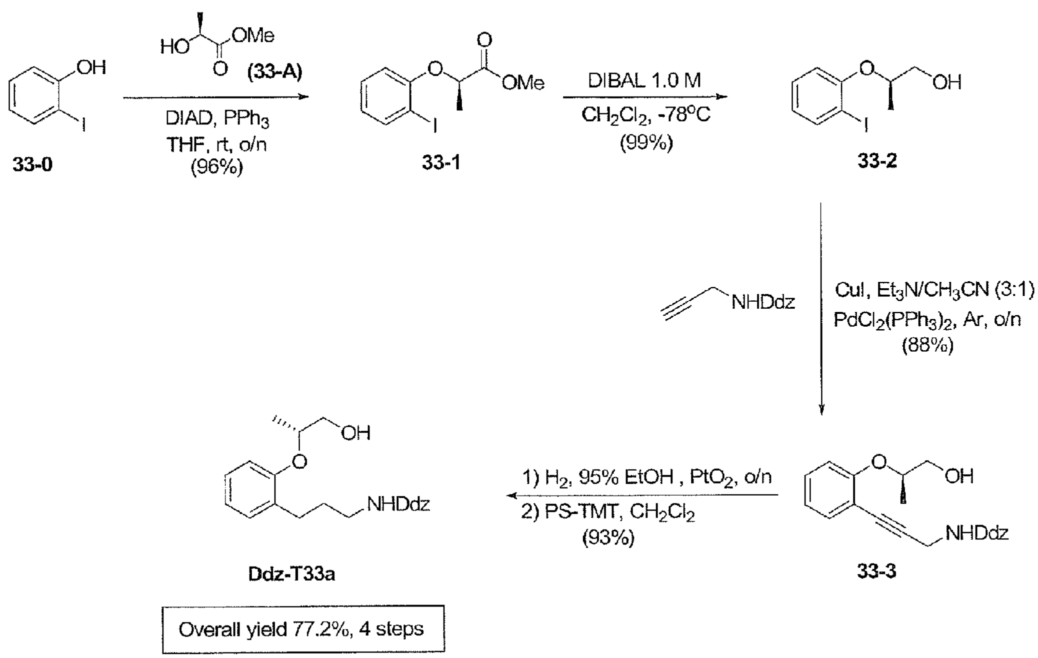
TLC (100% EtOAc; detection: UV, CMA; R_f = 0.24).

^{1}H NMR ($CDCl_3$, ppm): 7.74 (1H, dd), 7.35 (1H, d), 6.72 (1H, d), 6.53-6.49 (2H, m), 3.61-3.29 (1H, m), 5.06 (1H, t), 4.25-4.01 (2H, m), 3.91-3.89 (2H, m), 3.73 (3H, s), 2.99 (2H, dd), 2.63 (2H, t), 1.71 (8H, broad), 1.53 (9H, s).

^{13}C NMR ($CDCl_3$, ppm): 163.8, 162.2, 161.0, 159.7, 155.9, 149.4, 130.0, 129.1, 128.0, 126.8, 110.8, 98.1, 80.9, 79.3, 69.7, 61.3, 55.5, 39.1, 29.3, 28.5, 26.7.

FIG. 11

Standard Procedure for the Synthesis of Tether T33a and T33b



[1]H NMR ($CDCl_3$) δ (ppm) 7.18-7.11 (m, 2H), 6.90 (m, 2H), 6.52 (m, 2H), 6.33(m, 1H), 5.09 (bt, 1H), 4.52 (m, 1H), 3.77 (s, 6H), 3.08 (bq, 2H), 2.64 (bt, 2H), 1.75 (m, 8H); 1.27 (bd, 3H), [13]C NMR ($CDCl_3$) δ 160.8, 155.5, 149.5, 131.2, 130.6, 127.4, 121.2, 113.3, 103.2, 98,4, 80.7, 74.8, 66.5, 55,4, 40.2, 30.6, 29.3, 29.2, 27.4, 16.1

FIG. 12A

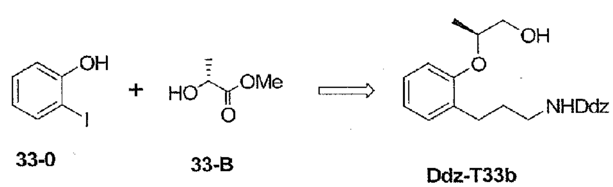
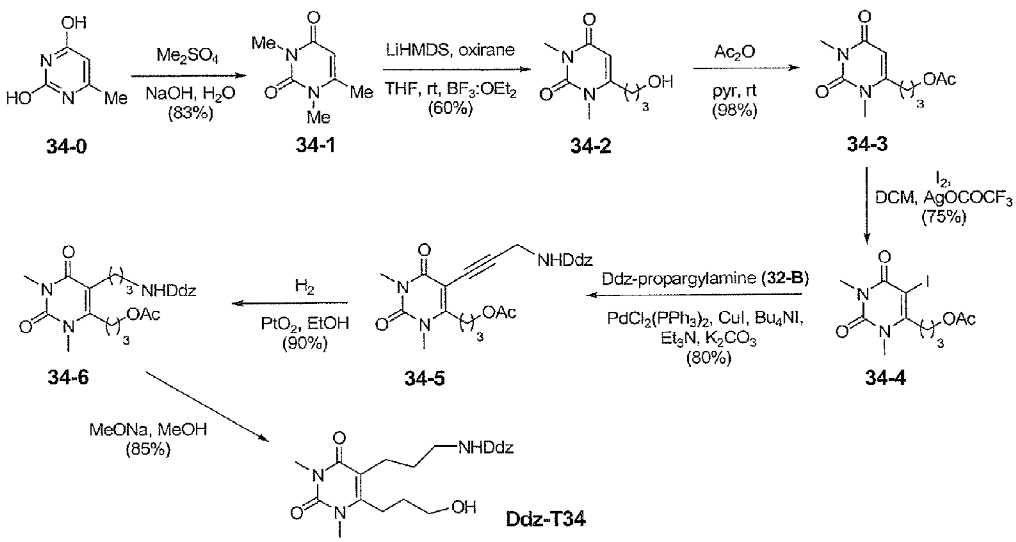


FIG. 12B

Standard Procedure for the Synthesis of Tether T34



TLC (100% EtOAc; detection: CMA, R_f = 0.5).

MW Calc. for $C_{24}H_{35}N_3O_7$, 477.55; MS Found $(M+H)^+$ 478.

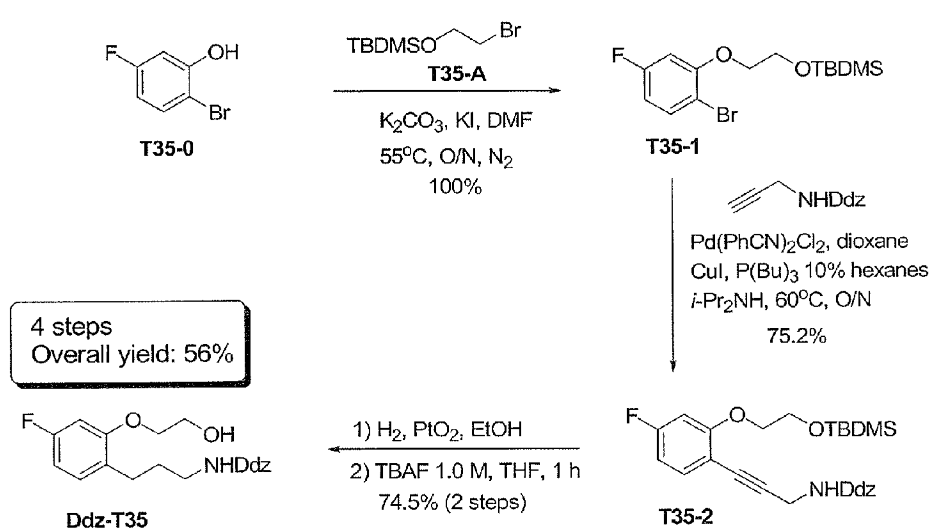
^{1}H NMR ($CDCl_3$) δ 1.62 (m, 2H), 1.70 (m, 8H), 2.43 (m, 2H), 2.67 (m, 2H), 3.07 (m, 2H), 3.34 (s, 3H), 3.43 (s, 3H), 3.61 (m, 2H), 3.75 (s, 6H), 5.40 (sb, 1H), 6.31 (s, 1H), 6.49 (s, 2H)

^{13}C NMR ($CDCl_3$) δ23.25 (CH_2), 25.97 (CH_2), 28.56 (CH_3), 39.31 (CH_3), 30.09 (CH_3), 31.25 (CH_2), 32.19 (CH_2), 40.16 (CH_2), 55.47 (CH_3), 61.38 (CH_2), 80.65 (Cq), 99.38 (Cq), 103.17 (Cq), 111.01(Cq), 149, 60 (Cq), 151.33 (Cq), 152.46 (Cq), 160.80 (Cq).

HPLC (standard gradient) t_R: 6.68 min.

FIG. 13

Standard Procedure for the Synthesis of Tether T35



TLC (25/75 EtOAc/Hex; detection: UV, ninhydrin; R_f = 0.03)

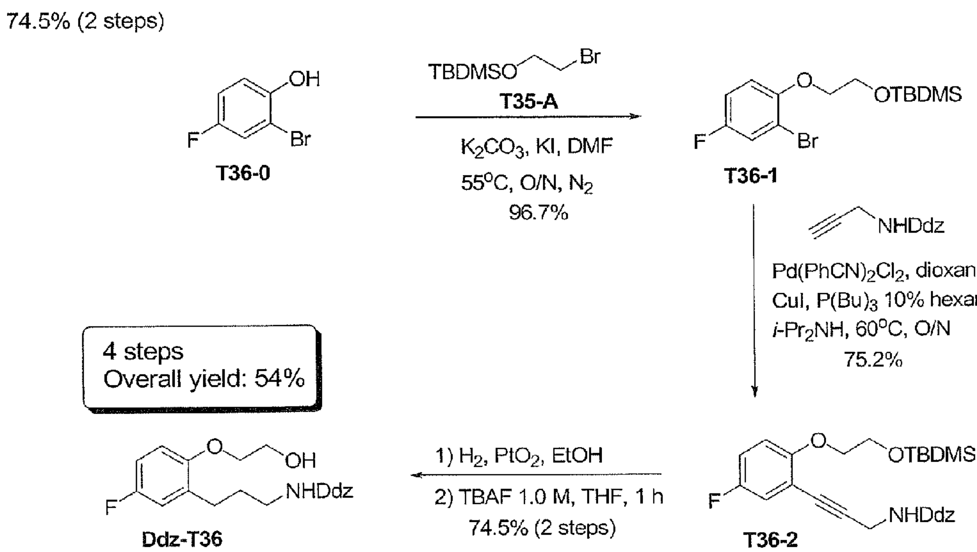
^{1}H NMR ($CDCl_3$): δ 7.06-7.00 (bt, 1H), 6.61-6.52 (m, 4H), 6.35 (m, 1H), 5.12 (bt, 1H), 4.03 (m, 2H), 3.95 (m, 2H), 3.77 (s, 6H), 3.11-3.04 (bq, 2H), 2.60 (bt, 2H), 1.75 (m, 8H)

^{13}C NMR ($CDCl_3$): δ 163.9, 160.9, 160.6, 157.6, 157.5, 155.6, 149.5, 130.8, 130.6, 125.9, 107.26, 106.9, 103.2, 98,4, 80.8, 77.5, 69.9, 61,3, 60.9, 60.6, 55,4, 40.3, 30.4, 29.3, 26.9,

HPLC (standard gradient): t_R = 8.37 min

FIG. 14

Standard Procedure for the Synthesis of Tether T36



TLC: (25/75 EtOAc/Hex; detection: UV, ninhydrin; R_f = 0.03)

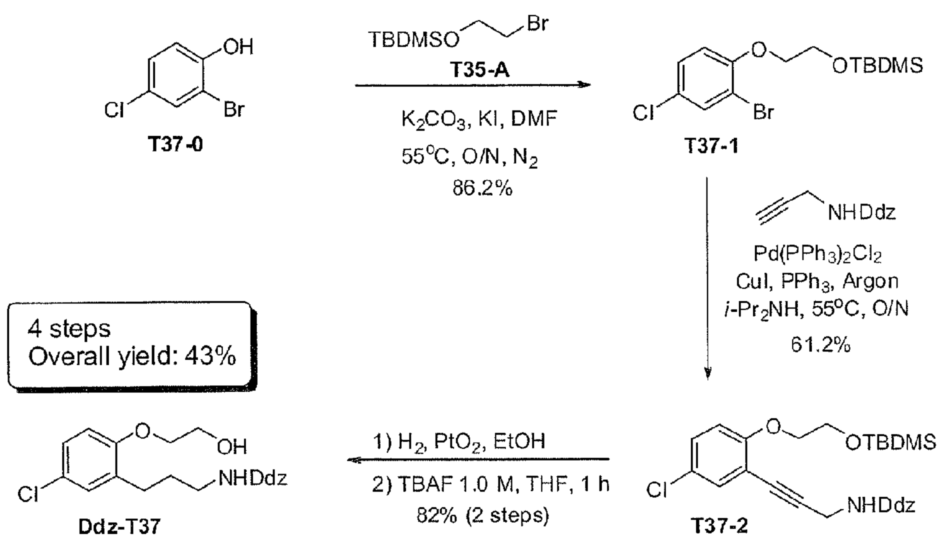
^{1}H NMR ($CDCl_3$) δ (ppm): 6.84-6.75 (m, 3H), 6.52 (bs, 2H), 6.34 (m, 1H), 5.17 (bt, 1H), 4.01 (m, 2H), 3.93 (m, 2H), 3.77 (s, 6H), 3.10 (bq, 2H), 2.63 (bt, 2H), 1.74 (m, 8H)

^{13}C NMR ($CDCl_3$) δ 160.9, 158.9, 155.8, 155.6, 152.9, 152.9, 149.5, 132.4, 132.3, 117.1, 116.8, 112.7, 112.6, 103.2, 98.4, 80.8, 70.4, 61.6, 55.5, 40.2, 30.3, 29.3, 27.4.

HPLC (standard gradient): t_R = 8.29 min

FIG. 15

Standard Procedure for the Synthesis of Tether T37



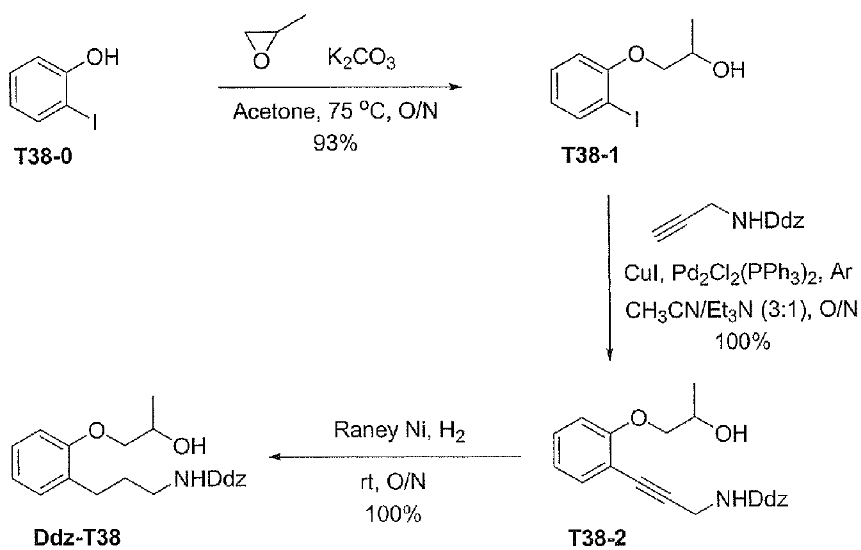
TLC (25/75 EtOAc/Hex; detection: UV, ninhydrin; $R_f = 0.03$)

^{1}H NMR ($CDCl_3$): δ 7.12-7.08 (bd, 2H), 6.76-6.73 (d, 1H), 6.52 (m, 2H), 6.33 (bs, 1H), 5.15 (bt, 1H), 4.02 (m, 2H), 3.95 (m, 2H), 3.79 (s, 6H), 3.09 (bq, 2H), 2.61 (bt, 2H), 1.74 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 160.8, 155.6, 155.4, 149.5, 132.4, 130.1, 127.0, 126.0, 112.8, 103.2, 98.4, 80.8, 70.0, 61.4, 55.5, 40.3, 30.2, 29.3, 24.5, 27.4

HPLC (standard gradient): t_R = 9.60 min

FIG. 16

Standard Procedure for the Synthesis of Tether T38

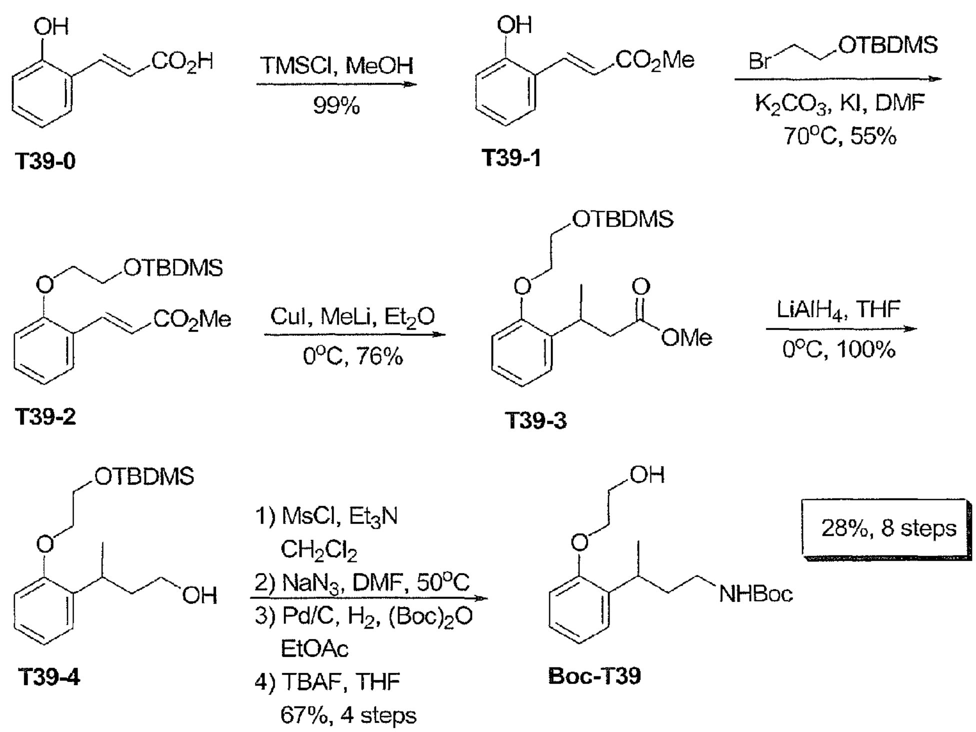


[1]H NMR ($CDCl_3$): δ 7.20-7.10, (m, 2H), 6.95-6.80 (m, 2H), 6.55 (bs, 2H), 6.35 (s, 1H), 5.18 (bt, 1H), 4.12 (m, 1H), 3.95 (m, 2H), 3.80 (s, 6H), 3.15 (bq, 2H), 2.65 (t, 2H), 1.98 (bs, 2H), 1.65 (bs, 6H), 1.25 (m, 3H).

[13]C NMR ($CDCl_3$): δ160.8, 156.6, 155.8, 149.6, 130.4, 127.5, 121.3, 111.7, 103.2, 98.4, 80.7, 73.5, 66.6, 55.5, 40.2, 30.5, 29.3, 29.1, 27.3, 19.5.

FIG. 17

Standard Procedure for the Synthesis of Tether T39



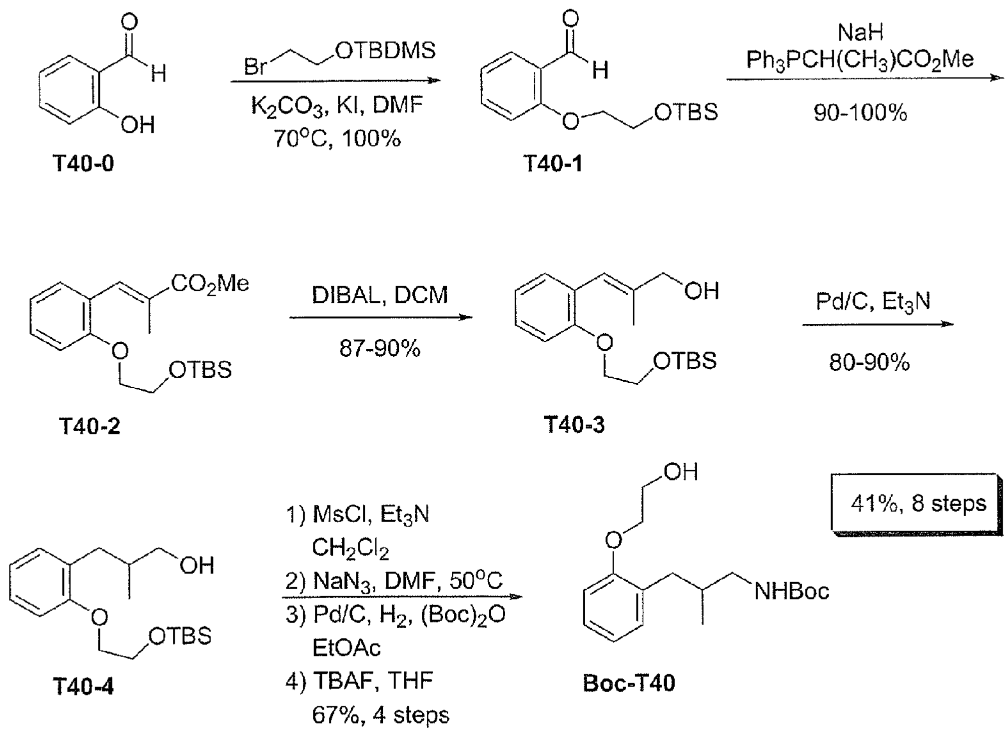
TLC (50% EtOAc, 50% Hex; detection: UV and CMA; R_f = 0.25)

^1H NMR ($CDCl_3$, ppm): 7.11-7.08 (2H, m), 6.86 (1H, t), 6.76 (1H, d), 5.05 (1H, broad), 4.26-3.85 (4H, m), 3.22-3.07 (2H, m), 2.71 (1H, broad), 1.66-1.60 (2H, m), 1.33 (9H, s), 1.17 (3H, d).

^{13}C NMR ($CDCl_3$, ppm): 156.1, 135.0, 127.1, 127.0, 121.4, 111.7, 69.9, 61.5, 39.8, 38.4, 28.7, 20.7.

FIG. 18

Standard Procedure for the Synthesis of Tether T40



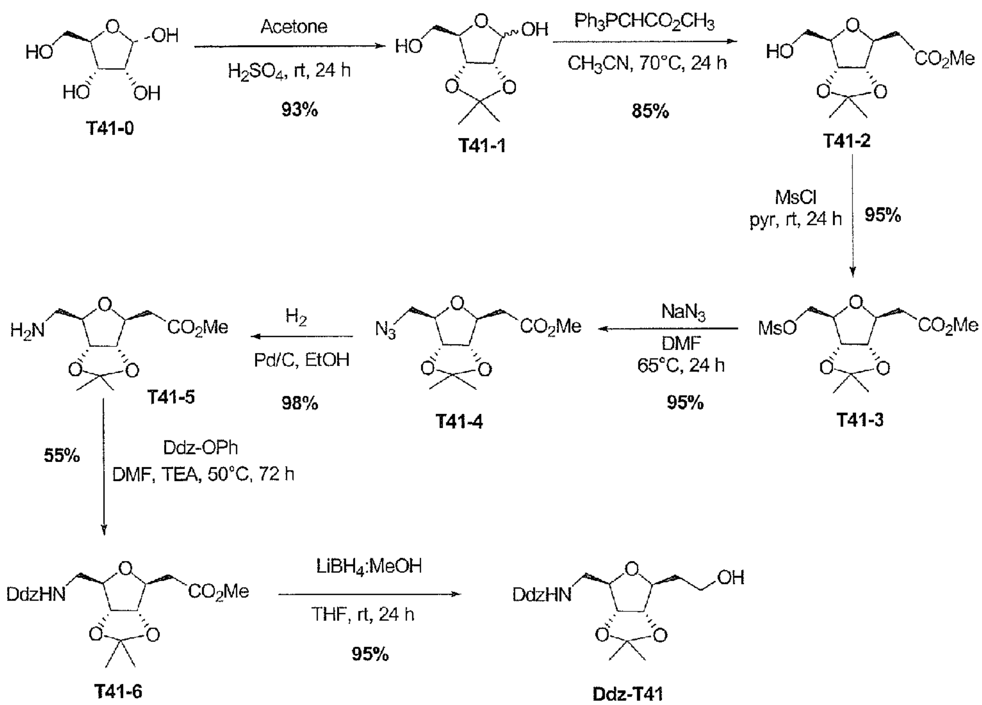
TLC (50% EtOAc, 50% Hex; detection: UV and CMA; $R_f = 0.25$)

^{1}H NMR ($CDCl_3$, ppm): 7.11-7.08 (2H, m), 6.86 (1H, t), 6.76 (1H, d), 5.05 (1H, broad), 4.26-3.85 (4H, m), 3.22-3.07 (2H, m), 2.71 (1H, broad), 1.66-1.60 (2H, m), 1.33 (9H, s), 1.17 (3H, d).

^{13}C NMR ($CDCl_3$, ppm): 156.1, 135.0, 127.1, 127.0, 121.4, 111.7, 69.9, 61.5, 39.8, 38.4, 28.7, 20.7.

FIG. 19

Standard Procedure for the Synthesis of Tether T41



TLC (100% EtOAc; detection: CMA; R_f = 0.5)

^{1}H NMR ($CDCl_3$) δ 1.23 (s, 3H), 1.49 (s, 3H), 1.69 (s, 3H), 1.74 (s, 3H), 1.90 (m, 2H), 2.35 (m, 1H), 3.35 (m, 2H), 3.76 (s, 6H), 3.92 (m, 2H), 4.40 (m, 2H), 5.10 (m, 1H), 6.15 (s, 1H), 6.25 (s, 2H).

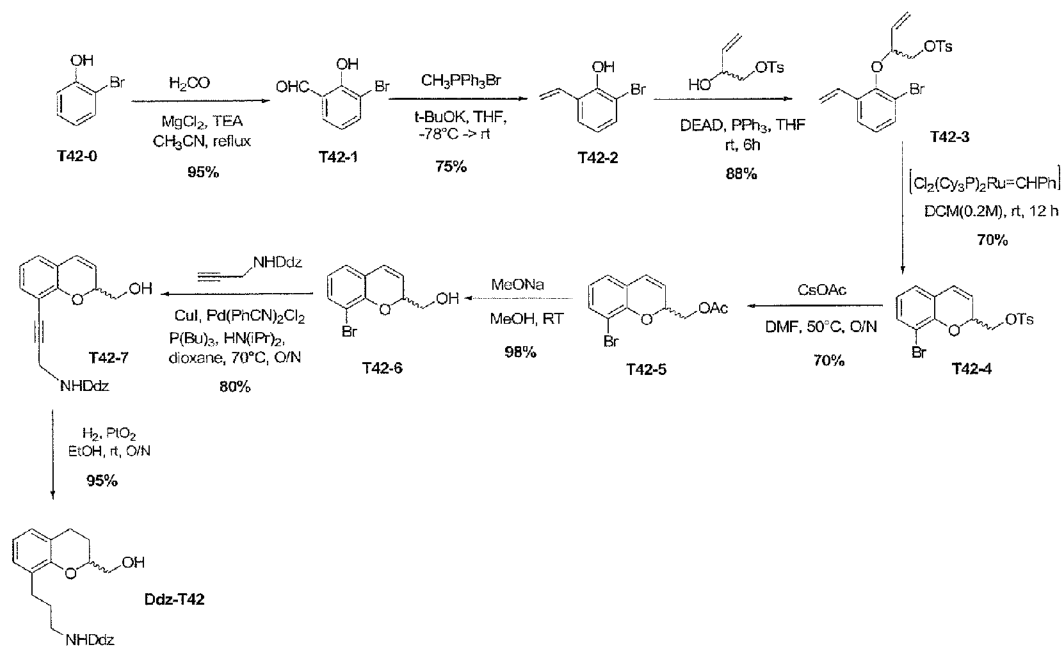
^{13}C NMR ($CDCl_3$) δ 25.52 ($\underline{C}H_3$), 27.53 ($\underline{C}H_3$), 28.88 ($\underline{C}H_3$), 29.61 ($\underline{C}H_3$), 35.92 ($\underline{C}H_2$), 42.62 ($\underline{C}H_2$), 55.43 ($\underline{C}H_3$), 60.60 ($\underline{C}H_2$), 82.38 ($\underline{C}H$), 83.33 ($\underline{C}H$), 83.68 ($\underline{C}H$), 84.96 ($\underline{C}H$), 98.26 ($\underline{C}H$), 103.23 ($\underline{C}H$), 118.3 ($\underline{C}$q), 149.50 ($\underline{C}$q), 156.20 ($\underline{C}$q), 160, 02 ($\underline{C}$q)

HPLC (standard gradient): t_R = 6.64 min

MS: M+H found: 439

FIG. 20

Standard Procedure for the Synthesis of Tether T42



[1]H NMR (300 MHz, $CDCl_3$) δ 6.82-6.98 (m, 2H); 6.80-6.75 (m, 1H); 6.53 (s, 2H); 6.35 (t, 1H, 2 Hz); 5.23 (b, 1H); 4.08 (m, 1H); 3.90-3.68 (m, 8H); 3.20-2.97 (m, 2H); 2.95-53 (m, 4H); 2.0-1.63 (m, 10H).

[13]C NMR (75.5 MHz, $CDCl_3$) δ160.85; 155.56; 152.55; 149.56; 128.13; 127.77; 120.28; 103.22; 98.43; 80.72; 76.80; 65.76; 55.46; 40.23; 30.45; 29.34; 29.22; 27.10; 24.97; 23.94.

FIG. 21

Scheme 2: Thioester Strategy for Macrocycl`ic Compounds of the Present Invention

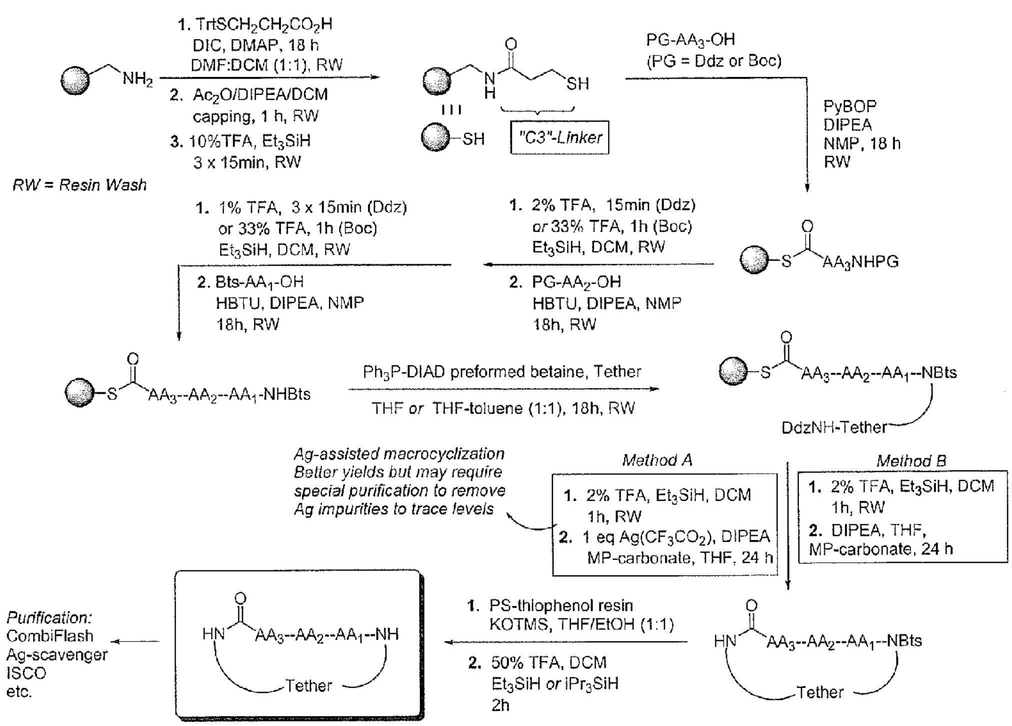
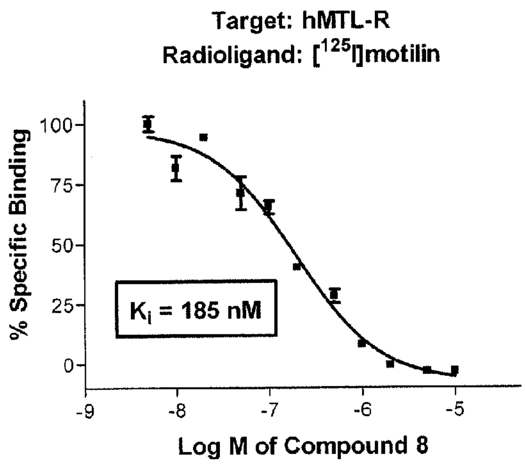
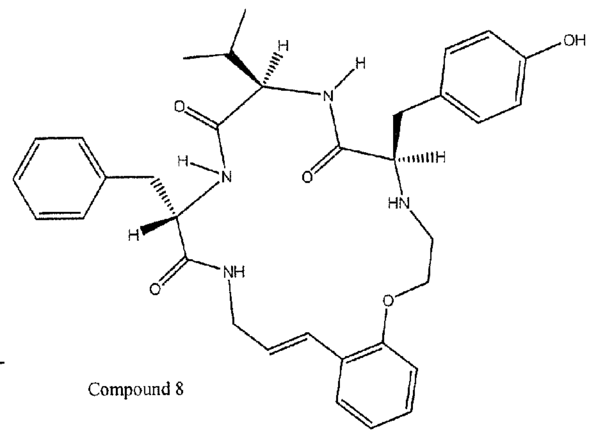


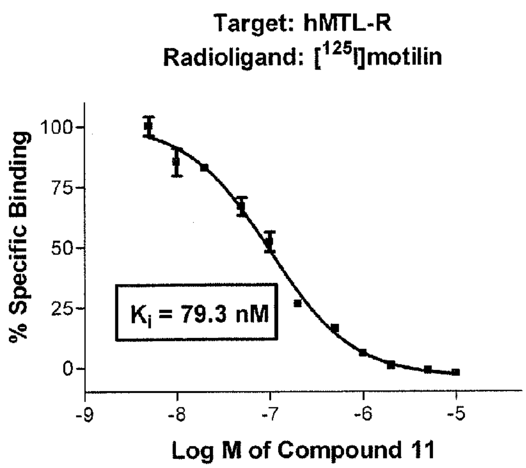
FIG. 22

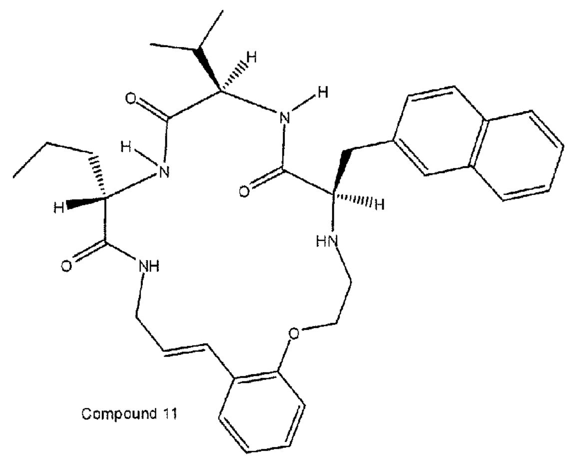




Compound 8

FIG. 23





Compound 11

FIG. 24

INTERMEDIATES FOR MACROCYCLIC COMPOUNDS

RELATED APPLICATION INFORMATION

This application is a continuation under 35 U.S.C. §120 of U.S. patent application Ser. No. 10/872,142, filed Jun. 18, 2004, now U.S. Pat. No. 7,521,420, which claims the benefit of U.S. Patent Application Ser. No. 60/479,223, filed Jun. 18, 2003. The disclosure of each application is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to novel conformationally-defined macrocyclic compounds, pharmaceutical compositions comprising same and intermediates used in their manufacture. More particularly, the invention relates to macrocyclic compounds that have been demonstrated to selectively antagonize the activity of the motilin receptor. The invention further relates to macrocyclic compounds useful as therapeutics for a range of gastrointestinal disorders, in particular those in which malfunction of gastric motility or increased motilin secretion is observed, such as hypermotilinemia, irritable bowel syndrome and dyspepsia.

BACKGROUND OF THE INVENTION

A number of peptide hormones are involved in the control of the different functions in the gastrointestinal (GI) tract, including absorption, secretion, blood flow and motility (Mulvihill, et al. in *Basic and Clinical Endocrinology,* 4[th] edition, Greenspan, F. S.; Baxter, J. D., eds., Appleton & Lange: Norwalk, Conn., 1994, pp 551-570). Since interactions between the brain and GI system are critical to the proper modulation of these functions, these peptides can be produced locally in the GI tract or distally in the CNS.

One of these peptide hormones, motilin, a linear 22-amino acid peptide, plays a critical regulatory role in the GI physiological system though governing of fasting gastrointestinal motor activity. As such, the peptide is periodically released from the duodenal mucosa during fasting in mammals, including humans. More precisely, motilin exerts a powerful effect on gastric motility through the contraction of gastrointestinal smooth muscle to stimulate gastric emptying, decrease intestinal transit time and initiate phase III of the migrating motor complex in the small bowel (Itoh, Z., Ed., *Motilin*, Academic Press: San Diego, Calif., 1990, ASIN: 0123757304; Nelson, D. K. *Dig. Dis. Sci.* 1996, 41, 2006-2015; Peeters, T. L.; Vantrappen, G.; Janssens, J. *Gastroenterology* 1980, 79, 716-719).

Motilin exerts these effects through receptors located predominantly on the human antrum and proximal duodenum, although its receptors are found in other regions of the GI tract as well (Peeters, T. L.; Bormans, V.; Vantrappen, G. *Regul. Pept.* 1988, 23, 171-182). Therefore, motilin hormone is involved in motility of both the upper and lower parts of the GI system (Williams et al. *Am. J. Physiol.* 1992, 262, G50-G55). In addition, motilin and its receptors have been found in the CNS and periphery, suggesting a physiological role in the nervous system that has not yet been definitively elucidated (Depoortere, I.; Peeters, T. L. *Am. J. Physiol.* 1997, 272, G994-999 and O'Donohue, T. L et al. *Peptides* 1981, 2, 467-477). For example, motilin receptors in the brain have been suggested to play a regulatory role in a number of CNS functions, including feeding and drinking behavior, micturition reflex, central and brain stem neuronal modulation and pituitary hormone secretion (Itoh, Z. Motilin and Clinical Applications. *Peptides* 1997, 18, 593-608; Asakawa, A.; Inui, A.; Momose, K.; et al., M. *Peptides* 1998, 19, 987-990 and Rosenfeld, D. J.; Garthwaite, T. L. *Physiol. Behav.* 1987, 39, 753-756). Physiological studies have provided confirmatory evidence that motilin can indeed have an effect on feeding behavior (Rosenfeld, D. J.; Garthwaite, T. L. *Phys. Behav.* 1987, 39, 735-736).

The recent identification and cloning of the human motilin receptor (WO 99/64436) has simplified and accelerated the search for agents which can modulate its activity for specific therapeutic purposes.

Due to the critical and direct involvement of motilin in control of gastric motility, agents that either diminish (hypomotility) or enhance (hypermotility) the activity at the motilin receptor, are a particularly attractive area for further investigation in the search for new effective pharmaceuticals towards these indications.

Peptidic agonists of the motilin receptor, which have clinical application for the treatment of hypomotility disorders, have been reported (U.S. Pat. Nos. 5,695,952; 5,721,353; 6,018,037; 6,380,158; 6,420,521, U.S. Appl. 2001/0041791, WO 98/42840; WO 01/00830 and WO 02/059141). Derivatives of erythromycin, commonly referred to as motilides, have also been reported as agonists of the motilin receptor (U.S. Pat. Nos. 4,920,102; 5,008,249; 5,175,150; 5,418,224; 5,470,961; 5,523,401, 5,554,605; 5,658,888; 5,854,407; 5,912,235; 6,100,239; 6,165,985; 6,403,775).

Antagonists of the motilin receptor are potentially extremely useful as therapeutic treatments for diseases associated with hypermotility and hypermotilinemia, including irritable bowel syndrome, dyspepsia, gastroesophogeal reflux disorders, Crohn's disease, ulcerative colitis, pancreatitis, infantile hypertrophic pyloric stenosis, diabetes mellitus, obesity, malabsorption syndrome, carcinoid syndrome, diarrhea, atrophic colitis or gastritis, gastrointestinal dumping syndrome, postgastroenterectomy syndrome, gastric stasis and eating disorders leading to obesity.

A variety of peptidic compounds have been described as antagonists of the motilin receptor (Depoortere, I.; Macielag, M. J.; Galdes, A.; Peeters, T. L. *Eur. J. Pharmacol.* 1995, 286, 241-247; U.S. Pat. Nos. 5,470,830; 6,255,285; 6,586,630; 6,720,433; U.S. 2003/0176643; WO 02/64623). These peptidic antagonists suffer from the known limitations of peptides as drug molecules, in particular poor oral bioavailability and degradative metabolism.

Cyclization of peptidic derivatives is a method employed to improve the properties of a linear peptide both with respect to metabolic stability and conformational freedom. Cyclic molecules tend to be more resistant to metabolic enzymes. Such cyclic tetrapeptide motilin antagonists have been reported (Haramura, M. et al *J. Med. Chem.* 2002, 45, 670-675, U.S. 2003/0191053; WO 02/16404).

Other motilin antagonists, which are non-peptidic and non-cyclic in nature have also been reported (U.S. Pat. Nos. 5,972,939; 6,384,031; 6,392,040; 6,423,714; 6,511,980; 6,624,165; 6,667,309; U.S. 2002/0111484; 2001/041701; 2002/0103238; 2001/0056106, 2002/0013352; 2003/0203906 and 2002/0002192)

The macrocyclic motilin antagonists of the present invention comprise elements of both peptidic and non-peptidic structures in a combination which has not been pursued for this application previously.

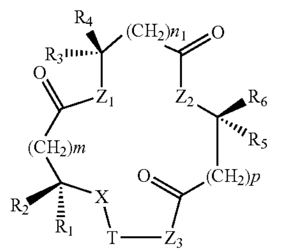
Indeed, the structural features of antagonists of the present invention are different. In particular, within the known motilin antagonists which are cyclic peptides, it was found that such derivatives containing D-amino acids were devoid of activity. In contrast, for the tripeptidomimetic compounds of the present invention, the D-stereochemistry is required for two of the three building elements.

The motilin antagonists of the present invention are also distinct from the prior art in that they comprise a tether element to fulfill the dual role of controlling conformations and providing additional sites for interaction either through hydrophobic interactions, hydrogen bonding or dipole-dipole interactions.

SUMMARY OF THE INVENTION

In a first aspect, the present invention is directed to compounds of formula (I):

(I)



and pharmaceutically acceptable salts, hydrates or solvates thereof wherein:

Z_1, Z_2 and Z_3 are independently selected from the group consisting of O, N and NR_{10}, wherein R_{10} is selected from the group consisting of hydrogen, lower alkyl, and substituted lower alkyl;

R_1 is independently selected from the group consisting of lower alkyl substituted with aryl, lower alkyl substituted with substituted aryl, lower alkyl substituted with heteroaryl and lower alkyl substituted with substituted heteroaryl;

R_2 is hydrogen;

R_3 is independently selected from the group consisting of alkyl and cycloalkyl with the proviso that when Z_1 is N, R_3 can form a four, five, six or seven-membered heterocyclic ring together with Z_1;

R_4 is hydrogen;

R_5 and R_6 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl and substituted heteroaryl, with the proviso that at least one of R_5 and R_6 is hydrogen;

X is selected from the group consisting of O, NR_8, and $N(R_9)_2^+$;

wherein R_8 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, formyl, acyl, carboxyalkyl, carboxylaryl, amido, sulfonyl, sulfonamido and amidino; and

R_9 is selected from the group consisting of hydrogen, lower alkyl, and substituted lower alkyl;

m, n_1 and p are independently selected from 0, 1 or 2; and

T is a bivalent radical of formula II:

$$—U—(CH_2)_d—W—Y—Z—(CH_2)_e— \qquad (II)$$

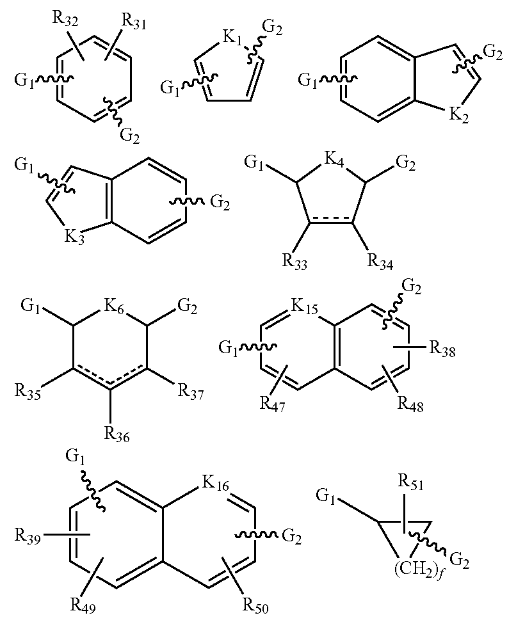
wherein d and e are independently selected from 0, 1, 2, 3, 4 or 5;

wherein U is bonded to X of formula (I) and is $—CH_2—$ or $—C(═O)—$;

wherein Y and Z are each optionally present;

W, Y and Z are independently selected from the group consisting of: —O—, $—NR_{28}—$, —S—, —SO—,

$—SO_2—$, —C(═O)—, —C(═O)—O—, —O—C(═O—O, —C(═O)—NH—, —NH—C(═O)—, $—SO_2—NH—$, $—NH—SO_2—$, $—CR_{29}R_{30}—$, —CH═CH— with a configuration Z or E, and —C≡C—, or from a ring structure independently selected from the group



wherein any carbon atom contained within said ring structure, can be replaced by a nitrogen atom, with the proviso that if said ring structure is a monocyclic ring structure, it does not comprise more than four nitrogen atoms and if said ring structure is a bicyclic ring structure, it does not comprise more than six nitrogen atoms;

G_1 and G_2 each independently represent a covalent bond or a bivalent radical selected from the group consisting of —O—, $—NR_{41}—$, —S—, —SO—, $—SO_2—$, —C(═O)—, —C(═O)—O—, —O—C(═O)—, —C(═O)NH—, —NH—C(═O)—, $—SO_2—NH—$, $—NH—SO_2—$, $—CR_{42}R_{43}—$, —CH═CH— with a configuration Z or E, and —C≡C—; with the proviso that G_1 is bonded closer to U than G_2;

K_1, K_2, K_3, K_4, K_6, K_{15} and K_{16} are independently selected from the group consisting of O, NR_{44} and S;

f is selected from 1, 2, 3, 4, 5 or 6;

R_{31}, R_{32}, R_{38}, R_{39}, R_{48} and R_{49} are independently selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, hydroxy, alkoxy, aryloxy, amino, halogen, formyl, acyl, carboxy, carboxyalkyl, carboxyaryl, amido, carbamoyl, guanidino, ureido, amidino, cyano, nitro, mercapto, sulfinyl, sulfonyl and sulfonamido; and

R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{47}, R_{50} and R_{51} are independently selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, hydroxy, alkoxy, aryloxy, oxo, amino, halogen, formyl, acyl, carboxy, carboxyalkyl, carboxyaryl, amido, carbamoyl, guanidino, ureido, amidino, cyano, nitro, mercapto, sulfinyl, sulfonyl and sulfonamido.

In a second aspect, the invention also proposes compounds of formula (I) which are antagonists of the motilin receptor.

In a third aspect, the invention proposes a method of treating a disorder associated with the motilin receptor or motility dysfunction in humans and other mammals, comprising administering a therapeutically effective amount of a compound of formula (I).

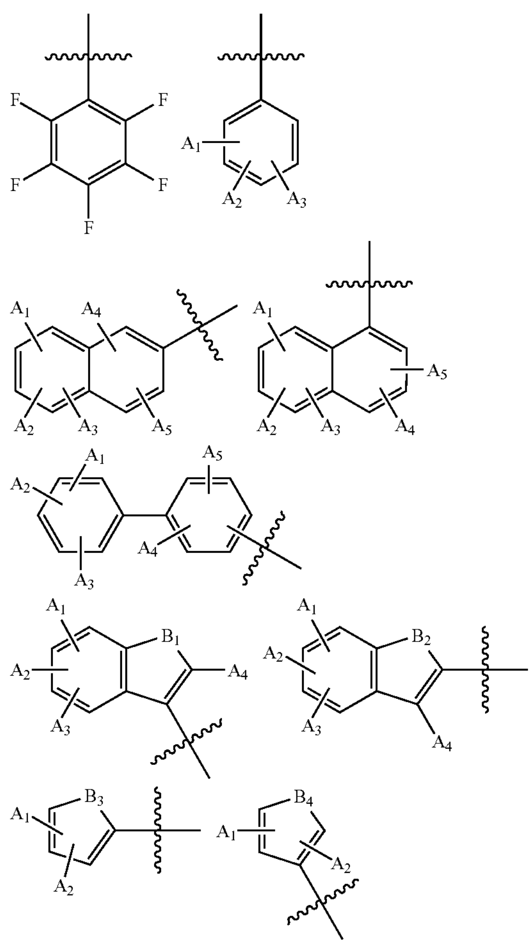
While the invention will be described in conjunction with example embodiments, it will be understood that it is not intended to limit the scope of the invention to such embodiment. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included as defined by the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

Preferably in formula (I), as depicted hereinabove, R_1 is selected from the group consisting of —$(CH_2)_qR_{11}$, and —$CHR_{12}R_{13}$

wherein q is 0, 1, 2 or 3; and

R_{11} and R_{12} are independently selected from a ring structure from the following group:



wherein any carbon atom in said ring structure can be replaced a nitrogen atom, with the proviso that if said ring structure is a monocyclic ring structure, it does not comprise more than four nitrogen atoms and if said ring structure is a bicyclic ring structure, it does not comprise more than six nitrogen atoms;

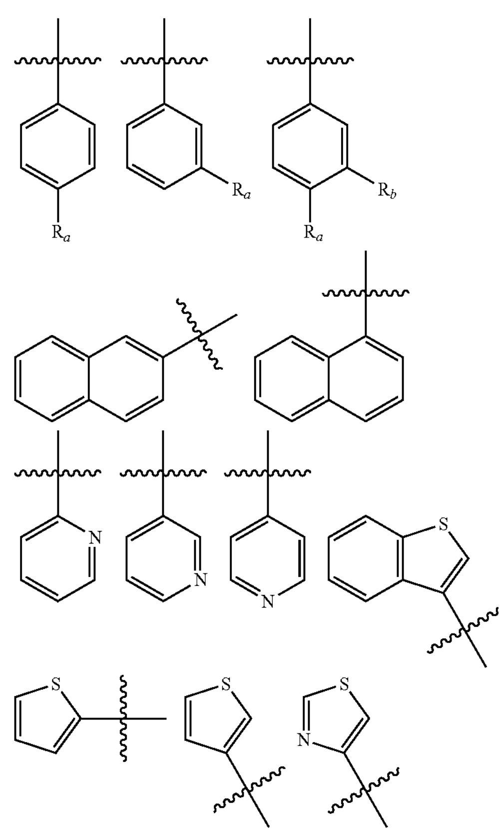
A_1, A_2, A_3, A_4 and A_5 are each optionally present and are independently selected from the group consisting of halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, hydroxy, alkoxy, aryloxy, amino, halogen, formyl, acyl, carboxy, carboxyalkyl, carboxyaryl, amido, carbamoyl, guanidino, ureido, amidino, cyano, nitro, mercapto, sulfinyl, sulfonyl and sulfonamido;

B_1, B_2, B_3, and B_4 are independently selected from NR_{14}, S or O, wherein R_{14} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, formyl, acyl, carboxyalkyl, carboxyaryl, amido, sulfonyl and sulfonamido;

R_{13} is as defined for as R_{11} and R_{12} or is selected from the group comprising lower alkyl, substituted lower alkyl, hydroxy, alkoxy, aryloxy, amino, carboxy, carboxyalkyl, carboxyaryl, and amido.

wherein A_1, A_2, A_3, A_4 and A_5 are most preferably selected from halogen, trifluororomethyl, C_{1-6} alkyl or C_{1-6} alkoxy.

Preferably, R_{11}, R_{12} and R_{13} are selected from the group consisting of:



wherein R_a and R_b are chosen from the group consisting of Cl, F, CF_3, OCH_3, OH, and $C(CH_3)_3$ and CH_3.

Also preferably, R_3 in formula (I), is selected from the group consisting of:

—$(CH_2)_sCH_3$, —$CH(CH_3)(CH_2)_tCH_3$, —$CH(OR_{15})CH_3$, —CH_2SCH_3—$CH_2CH_2SCH_3$, —$CH_2S(=O)CH_3$, —$CH_2CH_2S(=O)CH_3$, —$CH_2S(=O)_2CH_3$, —$CH_2CH_2S(=O)_2CH_3$, —$(CH_2)_uCH(CH_3)_2$, —$C(CH_3)_3$, and —$(CH_2)_v$—R_{21}, wherein:

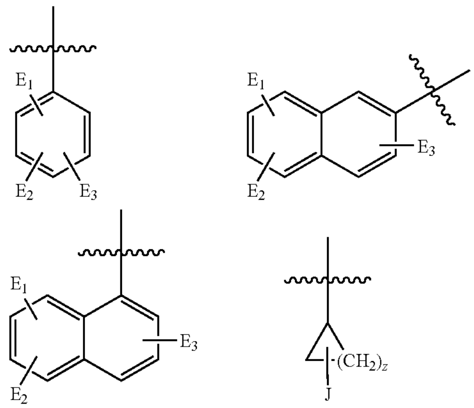
s and u are independently selected from 0, 1, 2, 3, 4 or 5;

t is independently selected from 1, 2, 3 or 4;

y is selected from 0, 1, 2, 3 or 4;

R_{15} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, formyl and acyl;

R_{21} is selected from a ring structure selected from the following group:



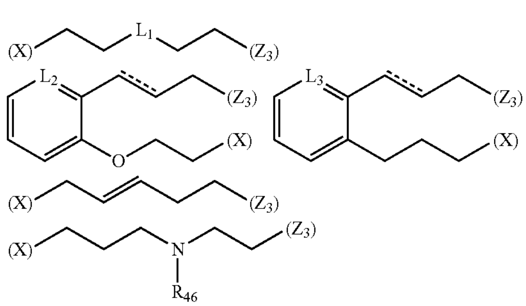
wherein any carbon atom in said ring structure can be replaced by a nitrogen atom, with the proviso that if said ring structure is a monocyclic ring structure, it does not comprise more than four nitrogen atoms and if said ring structure is a bicyclic ring structure, it does not comprise more than six nitrogen atoms;

z is selected from 1, 2, 3, 4 or 5;

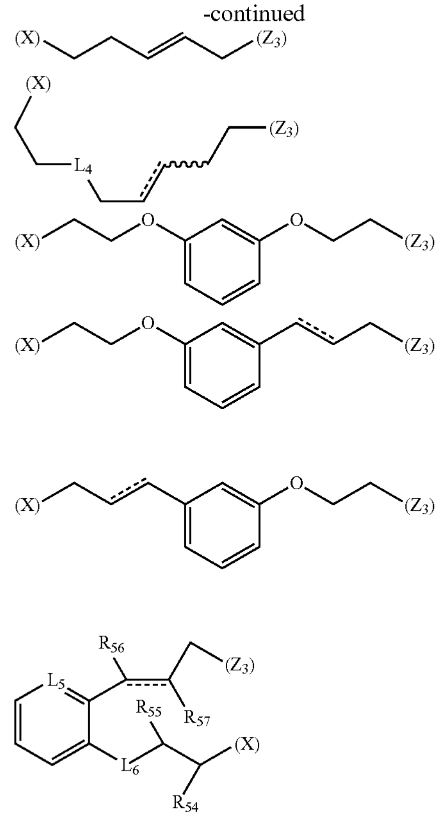
E_1, E_2 and E_3 are each optionally present and are independently selected from the group consisting of halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, hydroxy, alkoxy, aryloxy, amino, halogen, formyl, acyl, carboxy, carboxyalkyl, carboxyaryl, amido, carbamoyl, guanidino, ureido, amidino, cyano, nitro, mercapto, sulfinyl, sulfonyl and sulfonamido; and

J is optionally present and is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, hydroxy, alkoxy, aryloxy, oxo, amino, halogen, formyl, acyl, carboxy, carboxyalkyl, carboxyaryl, amido, carbamoyl, guanidino, ureido, amidino, mercapto, sulfinyl, sulfonyl and sulfonamido.

The tether portion (T) of formula (I) is preferably selected from the group consisting of:



-continued



wherein L_1 is O, NH or NMe; L_2 is CH or N; L_3 is CH or N; L_4 is O or CH_2; L_5 is CH or N L_6 is $CR_{52}R_{53}$ or O; R_{46} is H or CH_3;

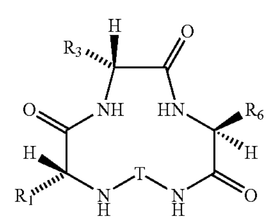
R_{52}, R_{53}, R_{54}, R_{55}, R_{56} and R_{57} are independently selected from hydrogen, lower alkyl, substituted lower alkyl, hydroxy, alkoxy, aryloxy, amino, and oxo; or R_{52} together with R_{53} or R_{54} together with R_{55} or R_{56} together with R_{57} can independently form a three to seven-membered cyclic ring comprising carbon, oxygen, sulfur and/or nitrogen atoms;

(X) is the site of a covalent bond to X in formula (I); and

(Z_3) is the site of a covalent bond to Z_3 in formula (I).

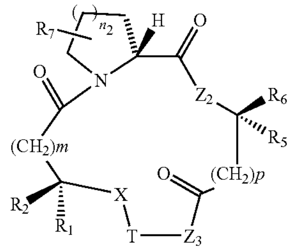
In a particularly preferred embodiment of the invention, there are provided compounds of formula (I) wherein m, n and p are 0, X, Z_1, Z_2 and Z_3 are NH and R_2, R_4 and R_5 are hydrogen, represented by formula (III):

(III)



According to another aspect of the invention, there are provided compounds of formula (I) wherein when Z_1 is a nitrogen atom, R_3 forms a four, five, six or seven-membered heterocyclic ring together with Z_1, represented by formula (IV):

(IV)



wherein said heterocyclic ring may contain a second nitrogen atom, or an oxygen, or sulfur atom;

n_2 is selected from 0, 1, 2 or 3

R_7 is optionally present and is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, hydroxy, alkoxy, aryloxy, oxo, amino, halogen, formyl, acyl, carboxy, carboxyalkyl, carboxyaryl, amido, carbamoyl, guanidino, ureido, amidino, mercapto, sulfinyl, sulfonyl and sulfonamido.

It is to be understood, that in the context of the present invention, the terms amino, guanidine, ureido and amidino encompass substituted derivatives thereof as well.

Preferably, the invention provides a method of treating a disorder associated with hypermotility or hypermotilinemia in humans and other mammals comprising administering a therapeutically effective amount of a compound of formula (I).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** depicts Scheme 1 presenting a general synthetic strategy to conformationally-defined macrocycles of the present invention.

FIG. **2** depicts the standard procedure for the synthesis of tether T8 of Example 16.

FIG. **3** depicts the standard procedure for the synthesis of tether T9 of Example 17.

FIG. **4** depicts the standard procedure for the synthesis of Ddz-propargylamine of Example 18.

FIG. **5**A depicts the standard procedure for the synthesis of tether T10 of Example 19.

FIG. **5**B depicts the second synthetic route to tether T10 of Example 19.

FIG. **6** depicts the standard procedure for the synthesis of Tether T11 of Example 20.

FIG. **7** depicts the standard procedure for the synthesis of tether T12 of Example 26.

FIG. **8** depicts the procedure for synthesis of PPh_3-DIAD adduct of Example 29-C.

FIG. **9** depicts the standard procedure for attachment of tethers via reductive amination of Example 30.

FIG. **10** depicts the standard procedure for the synthesis of tether T28 of Example 32.

FIG. **11** the standard procedure for the synthesis of tether T32 of Example 36.

FIGS. **12**A, **12**B depict the standard procedure for the synthesis of tether T33a and T33b of Example 37.

FIG. **13** depicts the standard procedure for the synthesis of tether T34 of Example 38.

FIG. **14** depicts the standard procedure for the synthesis of tether T35 of Example 39.

FIG. **15** depicts the standard procedure for the synthesis of tether T36 of Example 40.

FIG. **16** depicts the standard procedure for the synthesis of tether T37 of Example 41.

FIG. **17** depicts the standard procedure for the synthesis of tether T38 of Example 42.

Chiral T38 can be accessed through the use of asymmetric synthesis methods, resolution or chiral chromatography techniques available in the literature.

HPLC (standard gradient) t_R=8.46 min

Chiral material can be accessed by starting with the chiral epoxide. For example, the (S)-isomer of T38 was constructed in 89% overall yield from (S)-propylene oxide.

FIG. **18** depicts the standard procedure for the synthesis of tether T39 of Example 43. Chiral T39 can be accessed through the use of asymmetric synthesis methods, resolution or chiral chromatography techniques available in the literature.

FIG. **19** depicts the standard procedure for the synthesis of tether T40 of Example 44.

Chiral T40 can be accessed through the use of asymmetric synthesis methods, resolution or chiral chromatography techniques available in the literature.

FIG. **20** depicts the standard procedure for the synthesis of tether T41 of Example 45.

FIG. **21** depicts the standard procedure for the synthesis of tether T42 of Example 46.

FIG. **22** depicts Scheme 2 of the thioester strategy for macrocyclic compounds of the present invention.

FIG. **23** depicts the competitive binding curve for compound 8.

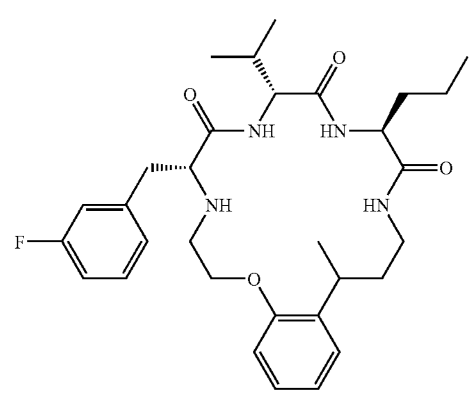
FIG. **24** depicts the competitive binding curve for compound 11

DESCRIPTION OF PREFERRED EMBODIMENTS

Although preferred embodiments of the present invention have been described in detail herein and illustrated in the accompanying structures, schemes and tables, it is to be understood that the invention is not limited to these precise embodiments and that various changes and modifications may be effected therein without departing from the scope or spirit of the present invention.

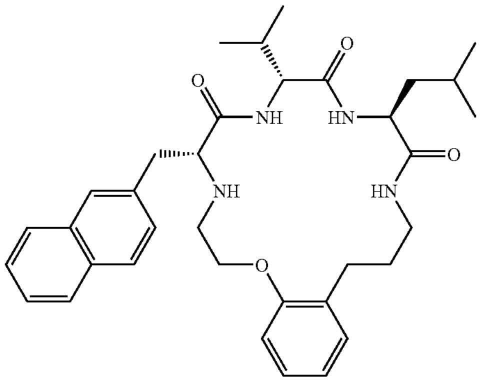
Specifically preferred compounds of the present invention, include, but are not limited to:

220

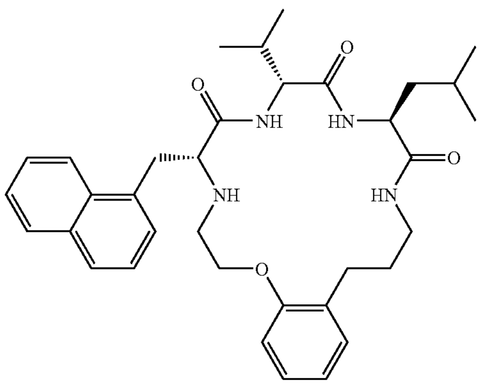


-continued

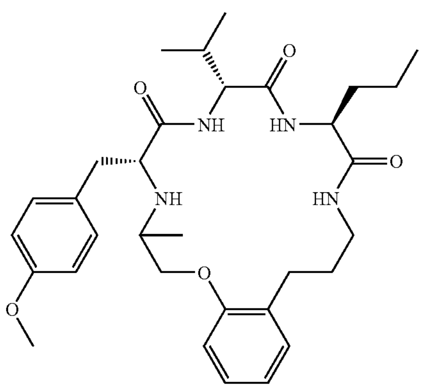
14



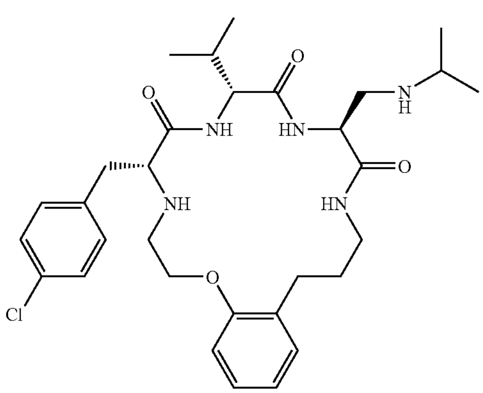
24



195

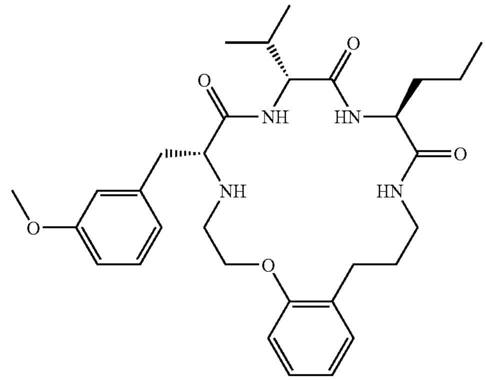


212

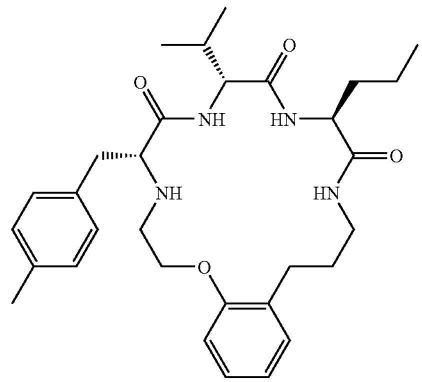


-continued

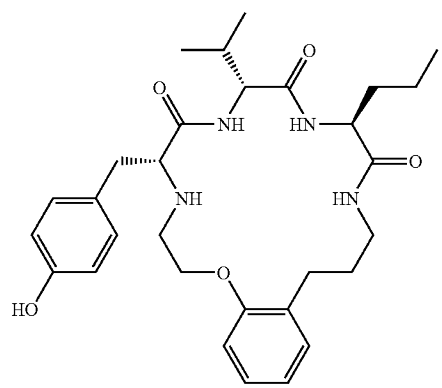
202



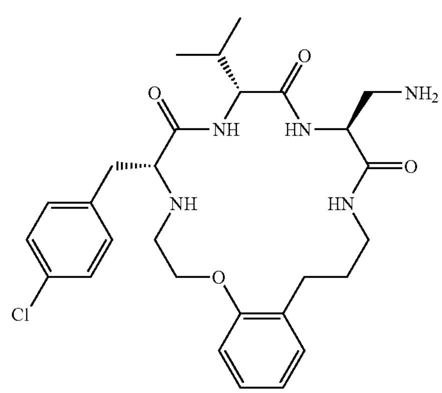
164



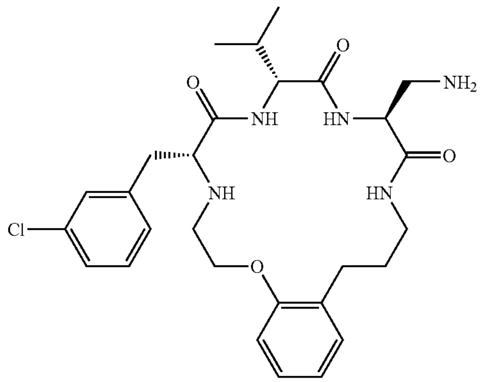
4



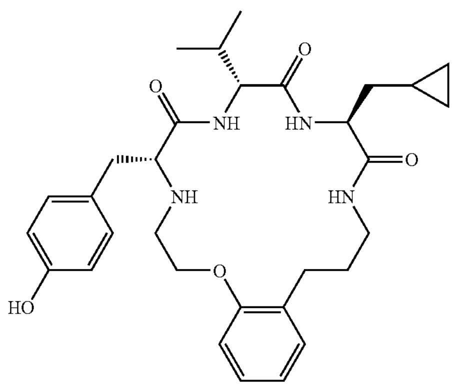
156



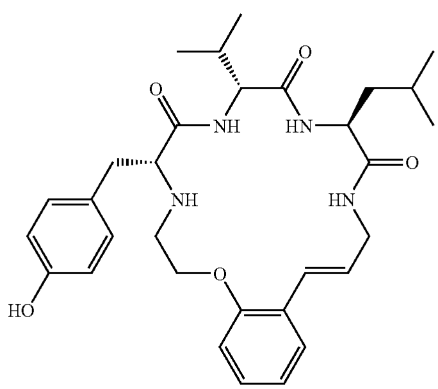
155



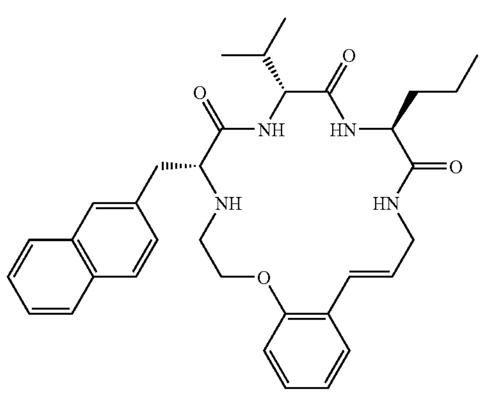
26



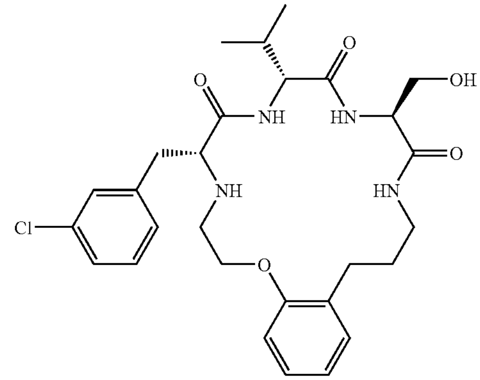
10



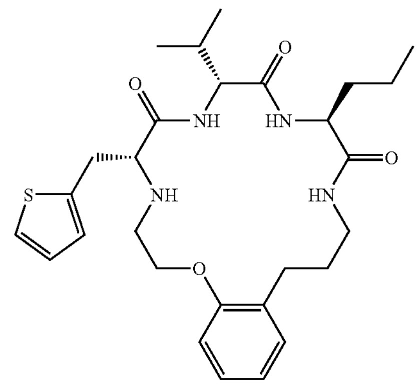
11



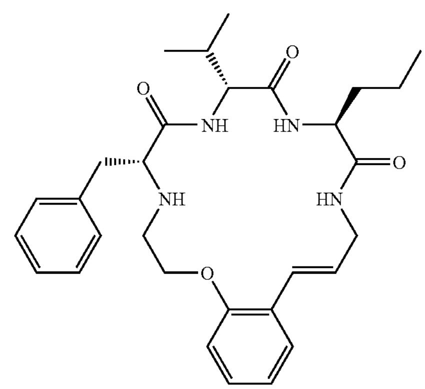
181



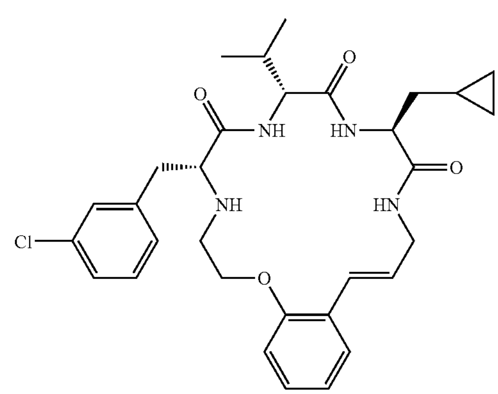
24



2

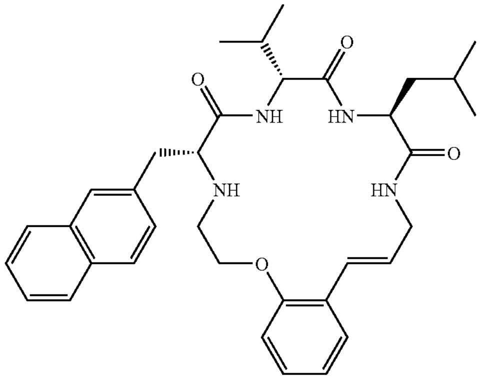


200

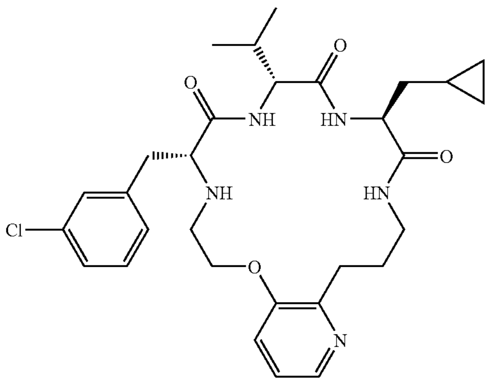


-continued

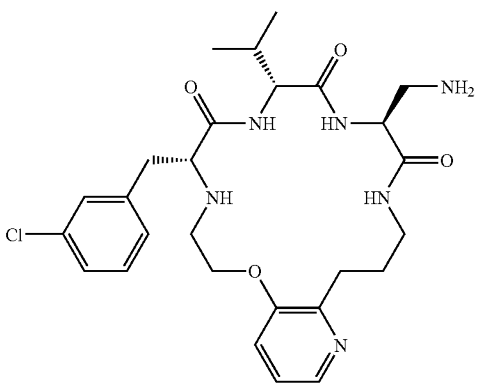
21



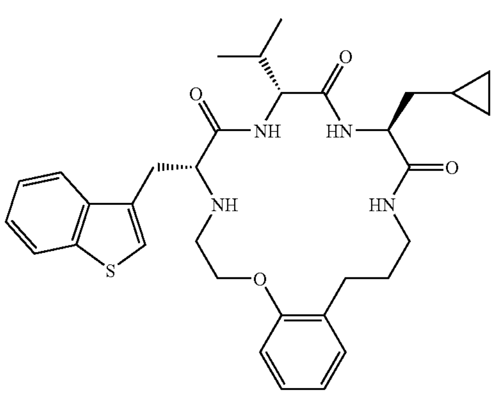
149



158

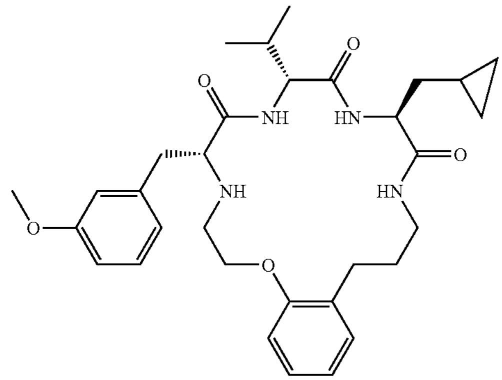


190

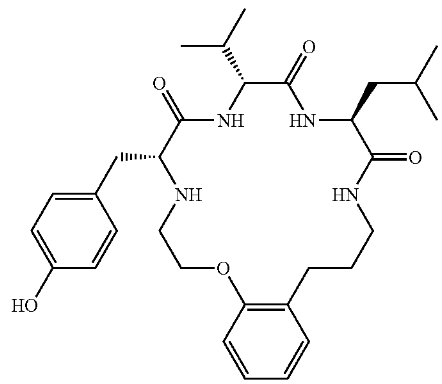


-continued

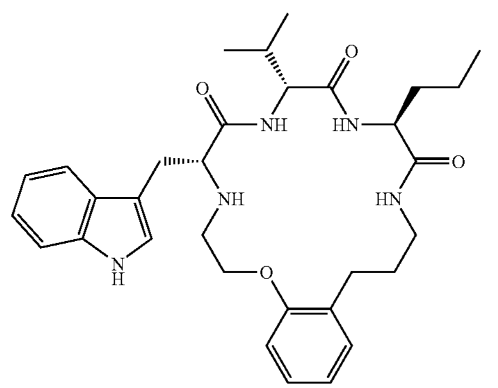
191



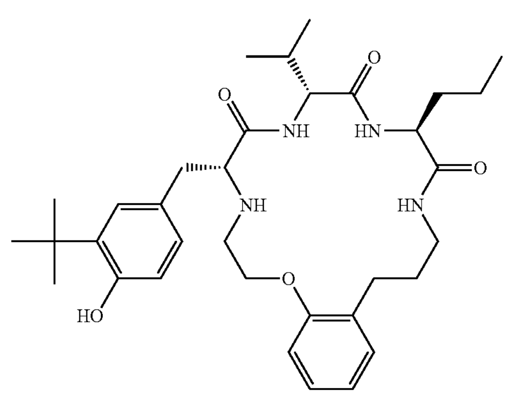
126



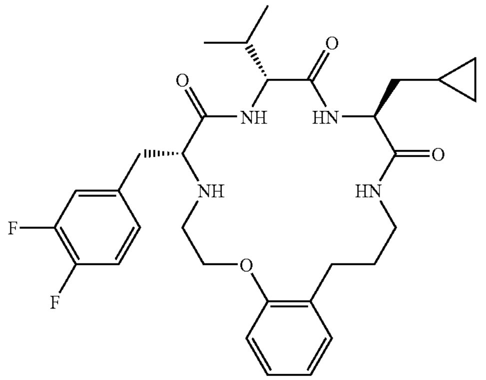
17



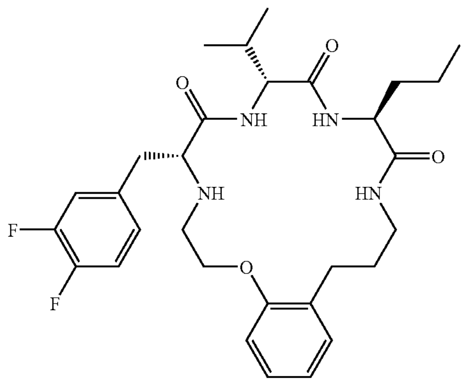
222



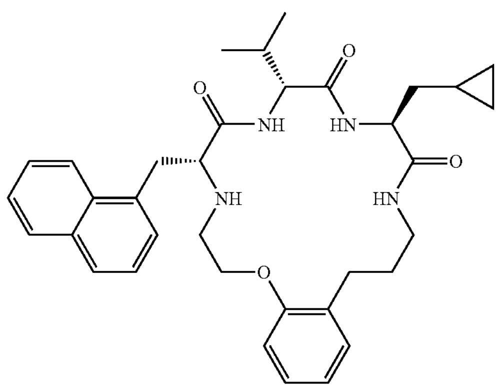
193



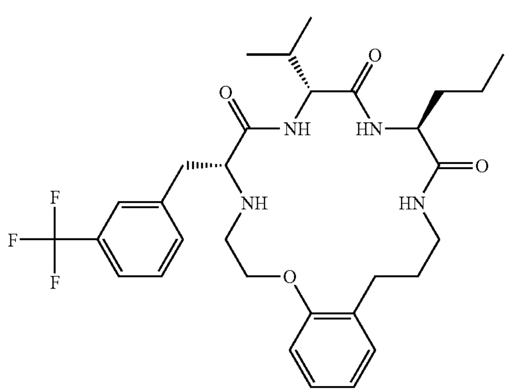
171



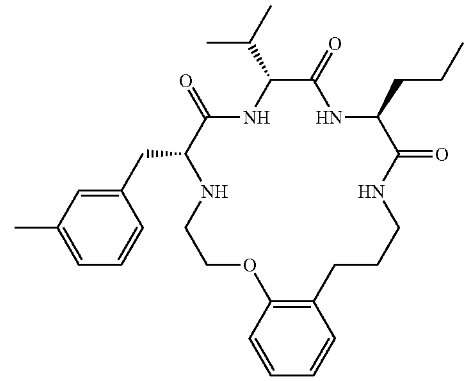
142



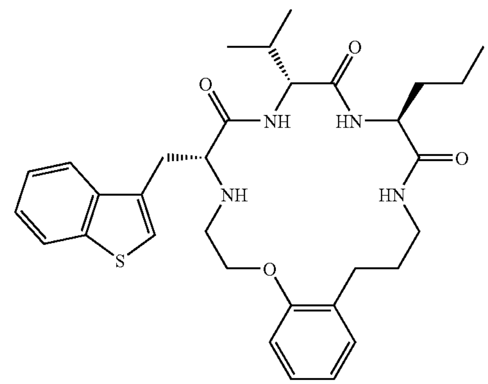
187



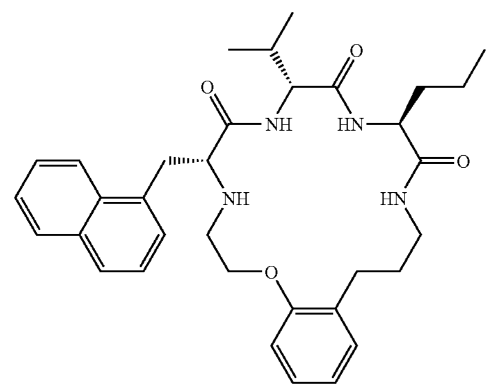
163



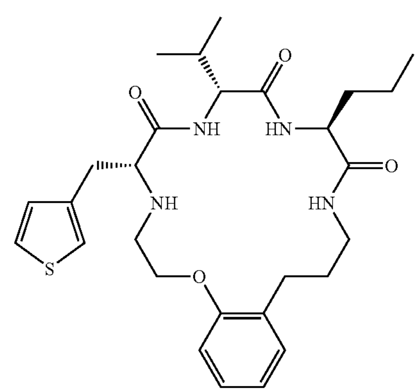
167



23

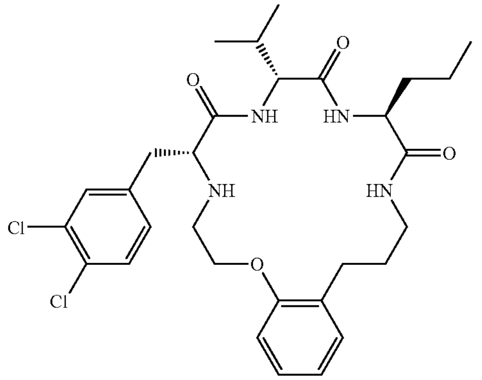


168

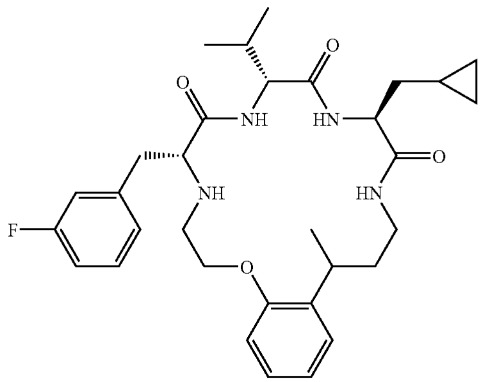


-continued

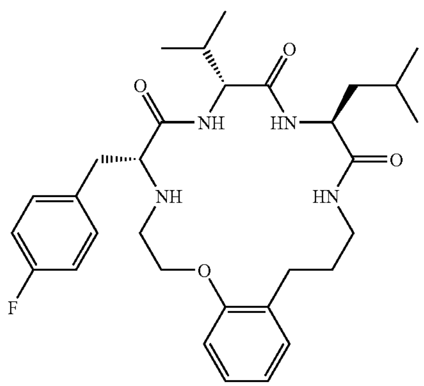
170



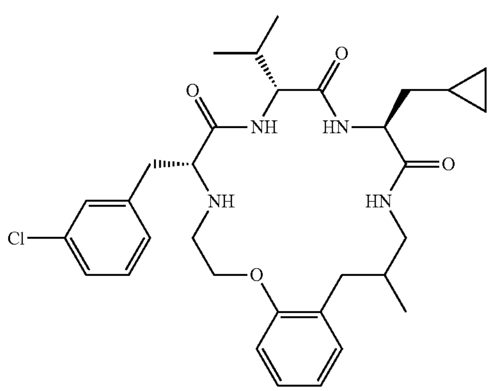
220



133

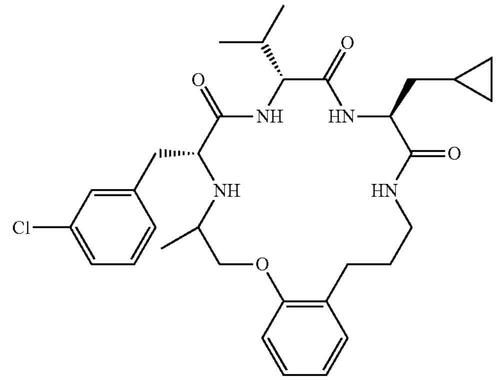


216

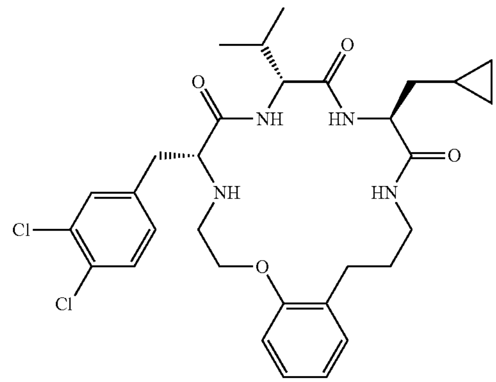


-continued

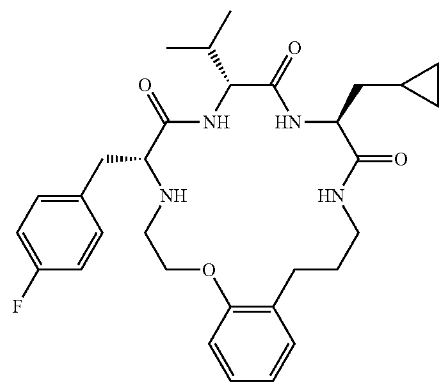
198



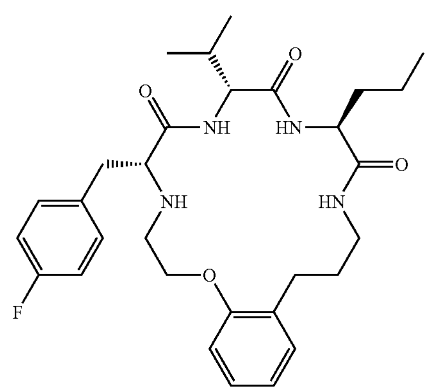
192



146

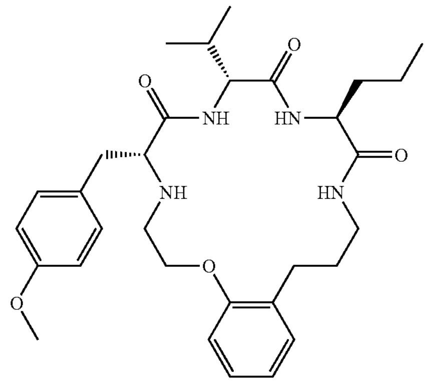


19

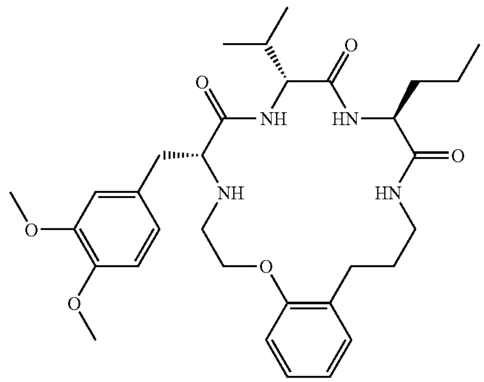


-continued

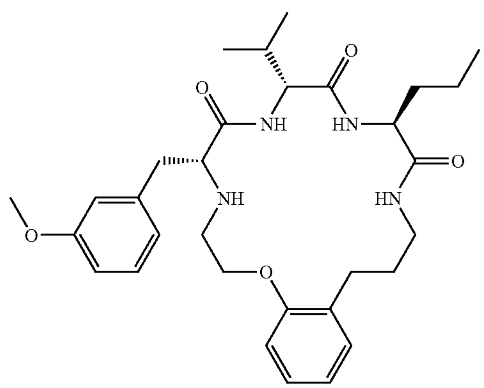
22



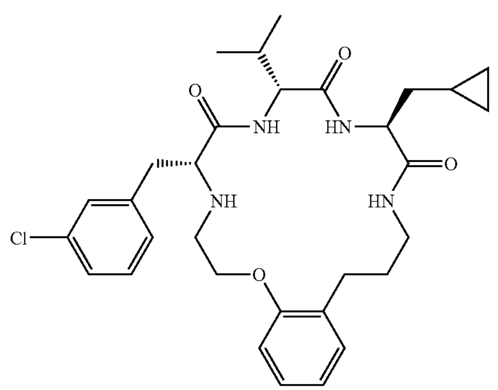
172



165

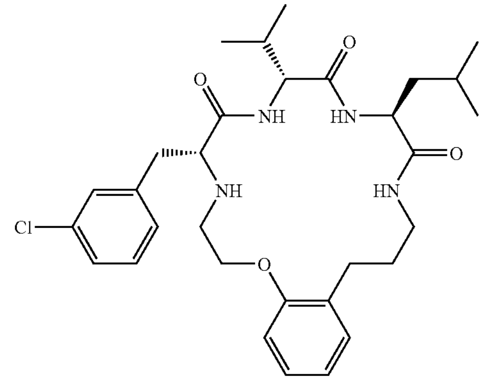


144

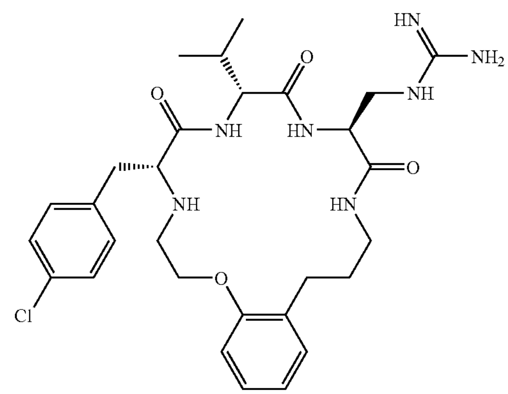


-continued

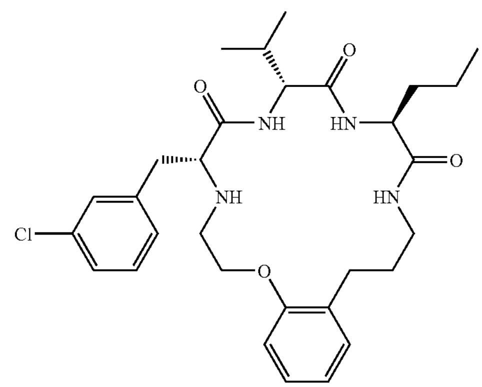
131



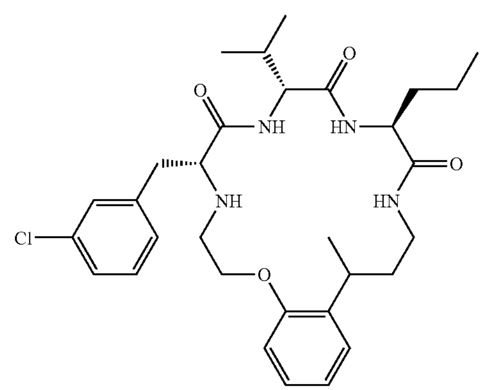
204



15

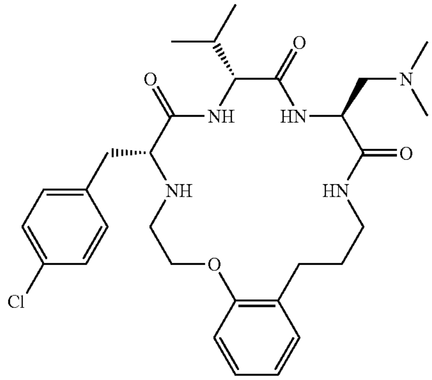


218

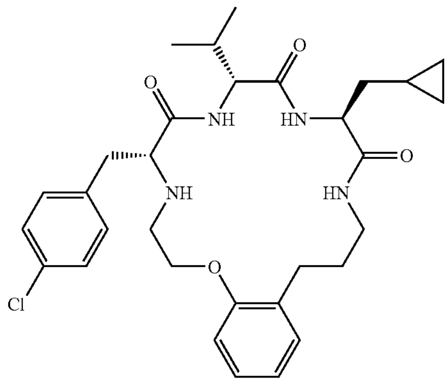


-continued

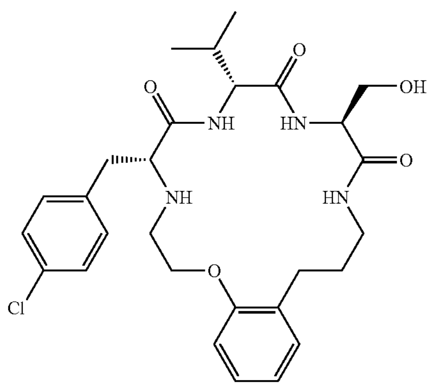
211



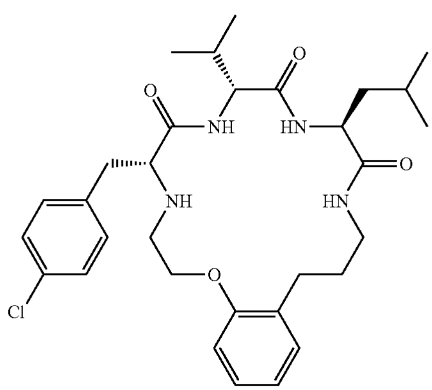
145



182

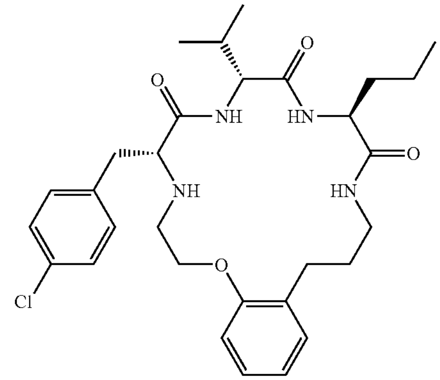


132

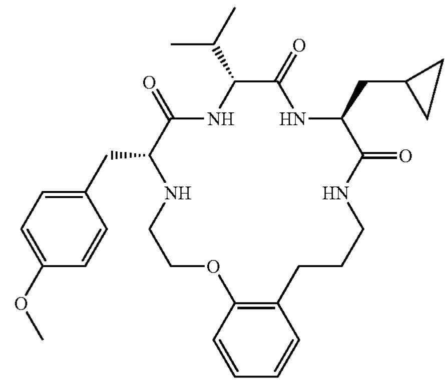


-continued

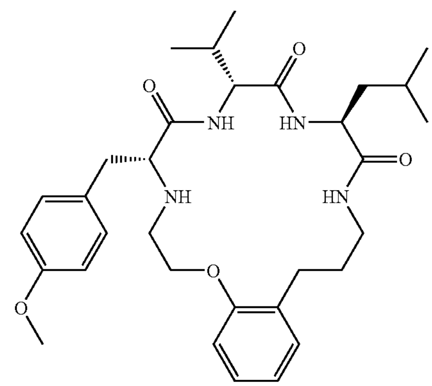
16



141

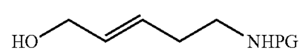


128

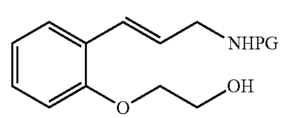


In addition to the preferred tethers (T) illustrated previously, other specific tethers employed for compounds of the invention are shown hereinbelow:

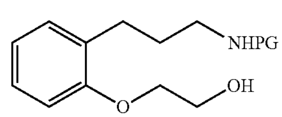
T2



T8

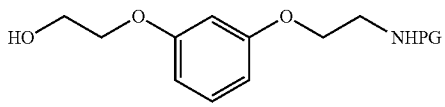


T9

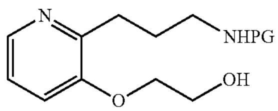


-continued

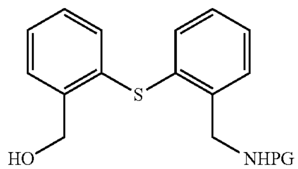
T10



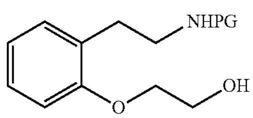
T11



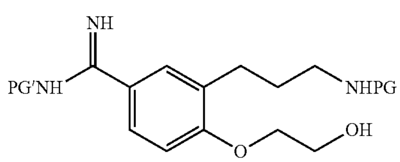
T12

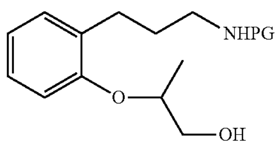


T28



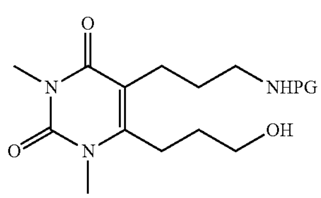
T32



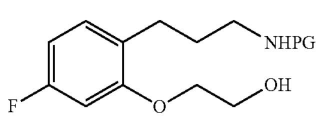


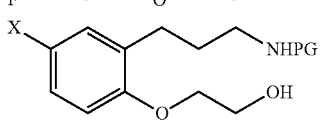
T33a [(R)-isomer]
T33b [(S)-isomer]

T34



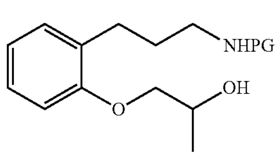
T35





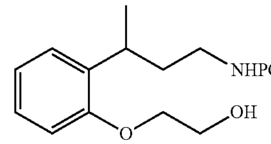
T36 (X = F)
T37 (X = Cl)

T38

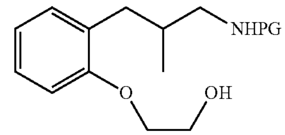


-continued

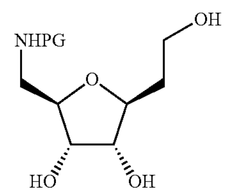
T39



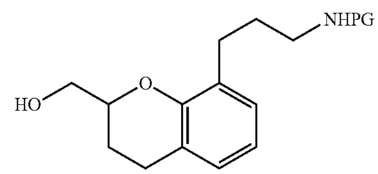
T40



T41



T42



PG and PG′ indicate a standard amine protecting group compatible with synthetic protocol, such as Boc, Ddz, Fmoc, or Alloc

In a preferred embodiment, the present invention is directed to a method of treating irritable bowel syndrome, dyspepsia, Crohn's disease, gastroesophogeal reflux disorders, ulcerative colitis, pancreatitis, infantile hypertrophic pyloric stenosis, carcinoid syndrome, malabsorption syndrome, diarrhea, diabetes mellitus, obesity, postgastroenterectomy syndrome, atrophic colitis or gastritis, gastric stasis, gastrointestinal dumping syndrome, celiac disease and eating disorders leading to obesity in humans and other mammals comprising administering a therapeutically effective amount of a compound of formula (I).

Synthetic Methods

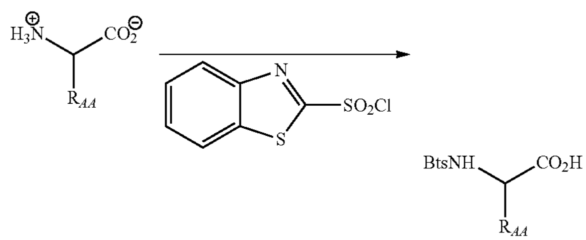
A. General Information

Reagents and solvents were of reagent quality or better and were used as obtained from various commercial suppliers unless otherwise noted. DMF, DCM and THF used are of DriSolv® (EM Science, now EMD Chemicals, Inc., part of Merck KgaA, Darmstadt, Germany) or synthesis grade quality except for (i) deprotection, (ii) resin capping reactions and (iii) washing. NMP used for the amino acid (AA) coupling reactions is of analytical grade. DMF was adequately degassed by placing under vacuum for a minimum of 30 min prior to use. Tyr(3tBu) was synthesized following the method reported in JP2000 44595. Cpa was made using literature methods (Tetrahedron: Asymmetry 2003, 14, 3575-3580) or obtained commercially. Boc- and Fmoc-protected amino acids and side chain protected derivatives, including those of N-methyl and unnatural amino acids, were obtained from commercial suppliers or synthesized through standard methodologies known to those in the art. Ddz-amino acids were either synthesized by standard procedures or obtained commercially from Orpegen (Heidelberg, Germany) or Advanced ChemTech (Louisville, Ky., USA). Bts-amino acids were synthesized as described in Example 6. Hydroxy acids were obtained from commercial suppliers or synthesized from the corresponding amino acids by literature methods. Analytical TLC was performed on pre-coated plates of silica gel 60F254 (0.25 mm thickness) containing a fluorescent indicator. The term "concentrated/evaporated under reduced pressure" indicates evaporation utilizing a rotary evaporator under either water aspirator pressure or the stronger vacuum provided by a mechanical oil vacuum pump as appropriate for the solvent being removed. "Dry pack" indicates chromatography on silica gel that has not been pre-treated with solvent, generally applied on larger scales for purifications where a large difference in R_f exists between the desired product and any impurities. For solid phase chemistry processes, "dried in the standard manner" is that the resin is dried first in air (1 h), and subsequently under vacuum (oil pump usually) until full dryness is attained (~30 min to O/N).

B. Synthetic Methods for Building Blocks of the Invention

Example 6

Standard Procedure for the Synthesis of Bts-Amino Acids



To a solution of the amino acid or amino acid derivative (0.1 mol, 1.0 eq) in 0.25 N sodium hydroxide (0.08 mol, 0.8 eq) with an initial pH of approximately 9.5 (pH meter) at rt, solid Bts-Cl (0.11 mol, 1.1 eq) was added in one portion. The resulting suspension was stirred vigorously for 2-3 d. The pH of the reaction should be adjusted with 5.0 N sodium hydroxide as required to remain within the range 9.5-10.0 during this time. Typically, the pH has to be adjusted every 20-30 min during the first 5 h. Once the pH stops dropping, it is an indication that the reaction is almost complete. This can be confirmed by TLC (EtOAc:MeOH, 95:5). Upon completion, the reaction mixture was washed with Et_2O. Washing is continued until the absence of non-polar impurities in the aqueous layer is confirmed by TLC (typically 3×100 mL). The aqueous solution was then cooled to 0° C., acidified to pH 2.0 with 1 N HCl until no additional cloudiness forms, and extracted with EtOAc (3×100 mL). Alternatively, a mixture of DCM and EtOAc may be used as the extraction solvent, depending on the solubility of the product obtained from different amino acids or derivatives. Note that DCM cannot be used solely as solvent because of the emulsion formed during extraction. The combined organic phases were washed with brine (2×150 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. DCM (1×) and hexanes (2×) were evaporated from the residue in order to ensure complete removal of the EtOAc and give the desired compound as a solid in 55-98% yield.

The following are modifications that have proven useful for certain amino acids: Gly, Ala, D-Ala, β-Ala and GABA: Use 1.5 eq of amino acid per eq of Bts-Cl, in order to prevent dibetsylation.

Met: Carry out the reaction under N_2 to prevent oxidation.

Gln and Asn: Due to the solubility of Bts-Gln and Bts-Asn, the work-up required is modified from the standard procedure: Upon completion of the reaction, the reaction mixture was washed with diethyl ether. Washing is continued until the absence of non-polar impurities in the aqueous layer is confirmed by TLC (typically 3×100 mL). The aqueous phase was then cooled to 0° C. and acidified to pH 2.0 with 6 N HCl. 6 N HCl was employed to minimize the volume of the solution due to the water solubility of Bts-Gln and Bts-Asn. (They are, in contrast, difficult to dissolve in DCM, EtOAc or chloroform.) The solution was maintained at 0° C. for 10 min and the product was collected by filtration as a white precipitate. The solid was washed with cold water (1×), cold brine (2×) and water (1×, 25° C.). The pH of this wash was taken, if it is not approximately 4, the solid was washed again with water. Finally, the solid was washed with cold EtOAc, then with cold Et_2O (2×), and finally dried under vacuum (oil pump) (83-85% yield).

C. General Synthetic Strategy to Conformationally-Defined Macrocycles of the Present Invention

The compounds of Formula I can be synthesized using traditional solution synthesis techniques or solid phase chemistry methods. In either, the construction involves four phases: first, synthesis of the building blocks, including one to four moieties, comprising recognition elements for the biological target receptor, plus one tether moiety, primarily for control and definition of conformation. These building blocks are assembled together, typically in a sequential fashion, in a second phase employing standard chemical transformations. The precursors from the assembly are then cyclized in the third stage to provide the macrocyclic structures. Finally, a post-cyclization processing stage involving removal of protecting groups and optional purification then provides the desired final compounds (see FIG. **1**). This method has been previously disclosed in WO 01/25257 and U.S. patent application Ser. No. 09/679,331. A general synthetic strategy is shown in FIG. **1**.

D. Procedures for the Synthesis of Representative Tethers of the Present Invention

The important tether component required for compounds of the invention are synthesized as described in WO01/25257, U.S. Provisional Pat. Appl. Ser. No. 60/491,248 or herein. A standard procedure for the synthesis of tether B is shown in FIG. **2**.

Step T8-1: Chlorotrimethylsilane (116 mL, 0.91 mol, 1.5 eq) was added to a suspension of 2-hydroxycinnamic acid (100 g, 0.61 mol, 1.0 eq) in MeOH (500 mL, HPLC grade) over 30 min at 0° C. The resulting mixture was stirred at rt O/N. The reaction was monitored by TLC (EtOAc/MeOH: 98/2). Heating the reaction mixture in a hot water can accelerate the process if necessary. After the reaction was completed, the reaction mixture was evaporated under reduced pressure to afford methyl 2-hydroxycinnamate as a white solid (108.5 g) in quantitative yield. The identity of this intermediate compound is confirmed by NMR. This reaction can be carried out on larger (kg) scale with similar results

Step T8-2: 3,4-Dihydro-2H-pyran (DHP, 140 mL, 1.54 mol, 2.52 eq) was added dropwise to 2-bromoethanol (108 mL, 1.51 mol, 2.5 eq) in a 2 L three-neck flask with mechanical stirring at 0° C. over 2 h. The resulting mixture was stirred for additional 1 h at rt. Methyl 2-hydroxycinnamate from Step T8-1 (108 g, 0.61 mol, 1.0 eq), potassium carbonate (92.2 g, 0.67 mol, 1.1 eq), potassium iodide (20 g, 0.12 mol, 0.2 eq) and DMF (300 mL, spectrometric grade) were added to the above flask. The reaction mixture was stirred at 70° C. (external temperature) for 24 h. The reaction was monitored by TLC (DCM/Et_2O: 95/5). The reaction was allowed to cool to rt and Et_2O (450 mL) was added. The inorganic salts were removed by filtration and washed with Et_2O (3×50 mL). The filtrate was diluted with hexanes (400 mL) and washed with water (3×500 mL), dried over $MgSO_4$, filtered and the filtrate evaporated under reduced pressure. The crude ester (desired product and excess Br—C_2H_4—OTHP) was used for the subsequent reduction without further purification.

Step T8-3: DIBAL (1.525 L, 1.525 mol, 2.5 eq, 1.0 M in DCM) was added slowly to a solution of the above crude ester from Step T8-2 (0.61 mol based on the theoretical yield) in anhydrous DCM (610 mL) at −35° C. with mechanical stirring over 1.5 h. The resulting mixture was stirred for 1.5 h at −35° C., then 1.5 h at 0° C. The reaction was monitored by TLC (hex/EtOAc:50/50). When complete, $Na_2SO_4.10H_2O$ (100 g, 0.5 eq) was slowly added; hydrogen evolution was observed, when it subsided water was added (100 mL). The mixture was warmed to rt and stirred for 10 min, then warmed to 40° C. with hot water and stirred under reflux for 20 min. The mixture was cooled to rt, diluted with DCM (600 mL), and the upper solution decanted into a filter. The solid that remained in the flask was washed with dichloromethane (5×500 mL) with mechanical stirring and filtered. The filtrate from each wash was checked by TLC, and additional washes performed if necessary to recover additional product. In an alternative work-up procedure, after dilution with DCM (600 mL), the mixture was filtered. The resulting solid was then continuously extracted with 0.5% TEA in dichloromethane using a Soxhlet extractor. Higher yield was typically obtained by this alternative procedure, although it does require more time. The filtrate was concentrated under reduced pressure and the residue purified by dry pack (EtOAc/hex/Et_3N: 20/80/0.5) to give the product alcohol as a yellowish oil (yield: 90%). The identity and purity were confirmed by NMR.

Step T8-4: To a mixture of the allylic alcohol from Step T8-3 (28 g, 0.100 mol, 1.0 eq) and collidine (0.110 mol, 1.1 eq) in 200 mL of anhydrous DMF under N_2 was added anhydrous LiCl (4.26 g, 0.100 mol, 1.0 eq.) dissolved in 100 mL of anhydrous DMF. The mixture was then cooled to 0° C., and MsCl (12.67 g, 0.110 mol, 1.1 eq., freshly distilled over P_2O_5), was added dropwise. The reaction was allowed to warm to rt and monitored by TLC (3:7 EtOAc/hex). When the reaction was complete, NaN_3 (32.7 g, 0.500 mol, 5.0 eq.) was added. The reaction mixture was stirred at rt O/N with progress followed by NMR. When the reaction was complete, the mixture is poured into an ice-cooled water bath, and extracted with diethyl ether (3×). The combined organic phases were then washed sequentially with citrate buffer (2×), saturated sodium bicarbonate (2×), and finally with brine (1×). The organic layer was dried with $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The allylic azide was obtained in 90% combined yield, and was of sufficient quality to use as such for the following step.

Step T8-5: PPh_3 (25.9 g, 0.099 mol, 1.5 eq) was added at 0° C. to a solution of the allylic azide from Step T8-4 (20.0 g, 0.066 mol, 1.0 eq.) in 100 mL of THF. The solution was stirred for 30 min at 0° C. and 20 h at rt. Water (12 mL) was then added and the resulting solution was heated at 60° C. for 4 h. The solution was cooled to rt, 2N HCl (15 mL) added and the mixture stirred for 90 min at 50° C. The separated organic phase was extracted with 0.05 N HCl (2×100 mL). The combined aqueous phase was washed with Et_2O (5×150 mL) and toluene (4×150 mL) (more extraction could be necessary, follow by TLC), which were combined and back-extracted with 0.05 N HCl (1×100 mL). This acidic aqueous phase from back-extraction was combined with the main aqueous phase and washed with ether (5×150 mL) again. The pH of the aqueous phase was then adjusted to 8-9 by the addition of sodium hydroxide (5 N). Care must be exercised to not adjust the pH above 9 due to the reaction conditions required by the next step. The aqueous phase was concentrated under reduced pressure (aspirator, then oil pump) or lyophilized to dryness. Toluene (2×) was added to the residue and then also evaporated under reduced pressure to remove traces of water. The crude product (desired amino alcohol along with inorganic salt) was used for the next reaction without further purification.

Step T8-6: A mixture of the crude amino alcohol from Step T8-5 (0.5 mol based on the theoretical yield), Ddz-OPh (174 g, 0.55 mol, 1.1 eq) and Et_3N (70 mL, 0.5 mol, 1.0 eq) in DMF (180 mL) was stirred for 24 h at 50° C. Additional DMF is added if required to solubilize all materials. The reaction was monitored by TLC (hex/EtOAc:50/50, ninhydrin detection). After the reaction was complete, the reaction mixture was diluted with Et_2O (1.5 L) and water (300 mL). The separated aqueous phase was extracted with Et_2O (2×150 mL). The combined organic phase was washed with water (3×500 mL) and brine (1×500 mL), dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The layers were monitored by TLC to ensure no product was lost into the aqueous layer. If so indicated, perform one or more additional extractions with Et_2O of the aqueous phase to recover this material. The crude product was purified by dry pack (recommended column conditions: EtOAc/hex/Et_3N: 35/65/0.5 to 65/35/0.5) to give the tether Ddz-T8 as a pale yellow syrup (yield: ~40%). The identity and purity of the product was confirmed by NMR.

^1H NMR (DMSO-d_6): 1.6 ppm (s, 6H, 2×CH3), 3.6-3.8 ppm (wide s, 10H, 2×OCH_3, 2×OCH_2), 3.95 ppm (triplet, 2H, CH_2N), 6-6.2 ppm (m, 2H, 2×CH), 6.2-6.5 ppm (m, 3H, 3×CH, aromatic), 6.6-7.6 ppm (m, 5H, aromatic).

A standard procedure for the synthesis of tether T9 is shown in FIG. **3**.

Tether T9 can also be synthesized from T8 by reduction as in step T9-3 or with other appropriate hydrogenation catalysts known to those in the art.

A standard procedure for the synthesis of Ddz propargylamine is shown in FIG. **4**,

In a dried three-neck flask, a solution of propargylamine (53.7 g, 0.975 mol, 1.5 eq) in degassed DMF (Drisolv, 388 mL) was treated with Ddz-N_3 (170.9 g, 0.65 mol, 1.0 eq), tetramethylguanidine (TMG, 81.4 mL, 0.65 mol, 1.0 eq) and DIPEA (113.1 mL, 0.65 mol, 1.0 eq) and stirred at 50° C. O/N. The reaction was monitored by TLC (conditions: 25/75 EtOAc/hex. R_f: 0.25; detection: UV, ninhydrin). Upon completion, DMF was evaporated under reduced pressure until dryness and the residue dissolved in Et_2O (1 L). The organic solution was washed sequentially with citrate buffer (pH 4.5, 3×), saturated aqueous sodium bicarbonate (2×), and brine (2×), then dried with $MgSO_4$, filtered and the filtrate evaporated under reduced pressure. A pale orange solid was obtained. This solid was triturated with 1% EtOAc in hex, then collected by filtration and dried under vacuum (oil pump) to provide the desired product (153.4 g, 85.2%).

A standard procedure for the synthesis of tether T10 is shown in FIG. **5**A.

Two alternative routes to this tether have been developed. The first synthetic approach proceeded starting from the commercially available monobenzoate of resorcinol (T10-0). Mitsunobu reaction under standard conditions with the protected amino alcohol from Example 9, followed by saponification of the benzoate provided T10-1 in good yield after recrystallization. Alkylation of the phenol with 2-bromoethanol using the optimized conditions shown permitted the desired product Ddz-T10 to be obtained after dry pack purification in 42% yield.

A second synthetic route to T10 is shown in FIG. **5**B.

From resorcinol, two successive Mitsunobu reactions are conducted with the appropriate two carbon synthons illustrated, themselves derived from 2-aminoethanol and ethylene glycol, respectively, through known protection methodologies. Lastly, deprotection of the silyl ether, also under standard conditions provided Boc-T10.

Although the yields in the two methods are comparable, the first required less mechanical manipulation and is preferred for larger scales.

A standard procedure for the synthesis of tether T11 is shown in FIG. **6**.

A standard procedure for the synthesis of tether T12 is shown in FIG. **7**.

In a 3-L flame-dried three-neck flask, a solution of (aminomethyl)phenylthiobenzyl alcohol (12-0, 96 g, 0.39 mol) in degassed DMF (1 L, 0.4 M) was prepared. To this was added $DdzN_3$ (0.95 eq), followed by TMG (0.39 mol, 49 mL). The reaction was stirred for 10 min, then DIPEA (68 mL, 0.39 mol) added. The mixture was heated at 50° C. under N_2 until TLC indicated no $DdzN_3$ remained (48 h typically). (TLC eluent: EtOAc:Hex 50:50; detection: ninhydrin). Upon completion, to the reaction mixture was added 3 L citrate buffer and the separated aqueous layer extracted with Et_2O (3×1500 mL). The combined organic phase was washed sequentially with citrate buffer (2×200 mL), water (2×200 mL) and brine (2×200 mL). The organic layer was dried over $MgSO_4$, filtered and the filtrate evaporated under reduced pressure. A dark orange oil was obtained, which was purified by dry-pack. For this procedure, the oil was first dissolved in EtOAc:Hex:DCM:TEA (20:80:1:0.5, v/v/v/v). At this point, a little extra DCM was sometimes required to ensure complete dissolution. The solution was loaded onto the column, then the column eluted with EtOAc:Hex:DCM:Et_3N (20:80:1:0.5) until all the impurities were separated out as indicated by TLC, paying particular attention to that closest to the desired product. The elution was then continued with EtOAc:Hex:Et_3N 30:70:0.5 (v/v/v) and finally with EtOAc:hexanes:Et_3N (50:50:0.5) to elute the desired product. After removal of the solvent from the fractions containing the product under reduced pressure, the residue was dissolved in the minimum amount of DCM, a three-fold larger volume of hexanes added, then the solvents again evaporated under reduced pressure. This treatment was repeated until an off-white foam was obtained. The latter solidified while drying under vacuum (oil pump). Alternatively, the material yielded a solid after sequential concentration with DCM (1×) and hexanes (2×). Tether Ddz-T12 was obtained as an off-white solid (85-90% yield).

Example 29

Standard Procedure for Attachment of Tethers Utilizing the Mitsunobu Reaction

Example 29-A

Using PPh_3-DIAD Isolated Adduct

To a 0.2 M solution of the appropriate tether (1.5 eq) in THF or THF-toluene (1:1) was added the PPh_3-DIAD (preformed by mixing equivalent amounts of the reagents and isolated by evaporation of solvent, see Example 29-C) adduct (1.0 eq.). The resultant mixture was manually agitated for 10 sec (the solution remained turbid), then added to the resin. Alternatively, the resin was added to the solution. The reaction suspension was agitated O/N (after ~5 min the mixture becomes limpid). The resin was filtered and washed 2×DCM, 1× toluene, 1× EtOH, 1× toluene, 1× (DCM/MeOH), 1× (THF/MeOH), 1× (DCM/MeOH), 1× (THF/MeOH), 2×DCM, then dried in the standard manner.

Example 29-B

Using "PPh_3-DIAD In Situ Procedure"

To a 0.2 M solution of the appropriate tether (4 eq) in THF or THF-toluene (1:1) was added triphenylphosphine (4 eq). The resultant mixture was manually shaken until a homogenous solution was obtained, then added to the resin. Alternatively, the resin (or IRORI™ MiniKans® (NEXUS Biosystems, Poway, Calif.), miniaturized microreactors, containing resin) was added to the solution. To this suspension was then added DIAD (3.9 eq) and the reaction agitated O/N. Note: Since the reaction is exothermic, for larger scales, the reaction should be cooled in an ice bath. In addition, an appropriate vent must be supplied to allow any pressure build-up to be released. The resin was filtered and washed DCM (2×), toluene (1×), EtOH (1×), toluene (1×), DCM/MeOH (1×), 1×THF/MeOH (1×), DCM/MeOH (1×), THF/MeOH (1×), 2×DCM, then dried in the standard manner.

A procedure for the synthesis of PPh_3-DIAD adduct is shown in FIG. **8**.

DIAD (1 eq) was added dropwise to a well-stirred solution of triphenylphosphine (1 eq) in THF (0.4 M) at 0° C. under nitrogen. The mixture was then maintained at 0° C. with stirring for 30 min. The white solid obtained was collected by filtration (use medium sized fritted filters), washed with cold anhydrous THF until the washes were colorless, and lastly washed once with anhydrous Et_2O. The white solid product was then vacuum-dried (oil pump) and stored under nitrogen. (Note: The PPh_3-DIAD adduct can be made in larger than immediately required quantity and stored under nitrogen; it is very important to store this reagent under anhydrous conditions.)

Example 30

Standard Procedure for Attachment of Tethers via Reductive Amination as shown in FIG. 9

In certain instances, the Mitsunobu process of Example 29 cannot be applied or is not efficient for incorporation of the tether. Hence, reductive amination has been developed as an alternative that can be employed for tether incorporation as illustrated hereinbelow for one of the preferred tethers. Similar chemistry can be used to incorporate other tethers of the present invention.

The Tether (30-2) with the amine protected as its Ddz derivative was efficiently oxidized to the corresponding aldehyde 30-2 using SO_3-pyr in DMSO-Et_3N-DCM. This aldehyde (0.14 mmol, 56 mg, 1.5 eq based upon loading of resin support) was dissolved in a 1:3 mixture of TMOF-MeOH (DriSolv, 4 mL) at rt. To this was added the resin containing the tripeptide (30-1, as its trifluoroacetic acid salt from the deprotection of the terminal amine), the mixture was agitated briefly to wet the resin, and then borane-pyridine complex (as the commercially available 8 M solution, 23 μL, 2 eq) was introduced to the suspension. The reaction was agitated O/N, then the resin filtered, washed with DCM (2×), THF (1×), DCM/MeOH [3:1] (1×), THF/MeOH [3:1] (1×), DCM (2×) and dried in the standard manner. Care must be taken to ensure that the desired resin bound product 30-3 is not contaminated with the dialkylated material. However, even if the reaction does not proceed to completion or if a small amount of the dialkylation side product is present, the material is of sufficient purity for the macrocyclization reaction.

A standard procedure for the synthesis of tether T28 is shown in FIG. **10**.

Henry reaction of 2-hydroxybenzaldehyde 28-0 provided 28-1 in 79% yield. This was followed by reduction first with sodium borohydride, then with catalytic hydrogenation, to give the amine, which was then protected as its Boc derivative, 28-2. Yields of these first two steps were lower on larger scales. Alkylation of 28-2 with the TBDMS ether of 2-bromoethanol, itself synthesized by standard methods, gave 28-3 in 74% yield. Deprotection of the silyl ether under standard conditions yielded the desired protected tether, Boc-T28. Alternative use of ethylene carbonate for the phenol alkylation to avoid the protection/deprotection steps, gave 73% yield.

A standard procedure for the synthesis of tether T32 is shown in FIG. **11**.

A standard procedure for the synthesis of tether T33a and T33b is shown in FIGS. **12**A and **12**B.

The construction to the (R)-isomer of this tether (T33a) was accomplished from 2-iodophenol (33-0) and (S)-methyl lactate (33-A). Mitsunobu reaction of 33-0 and 33

A proceeded with inversion of configuration in excellent yield to give 33-1. Reduction of the ester to the corresponding alcohol (33-2) also occurred in high yield and was followed by Sonagashira reaction with Ddz-propargylamine. The alkyne in the resulting coupling product, 33-3, was reduced with catalytic hydrogenation. Workup with scavenger resin provided the desired product, Ddz-T33a.

The synthesis of the (S)-enantiomer (Ddz-T33b) was carried out in an identical manner in comparable yield starting from (R)-methyl lactate (33-B). See FIG. **12**B.

Standard procedures for the synthesis of various tethers are shown in the figures: tether T34 (FIG. **13**), tether T35 (FIG. **14**), tether T36 (FIG. **15**), tether T37 (FIG. **16**), tether T38 (FIG. **17**), tether T39 (FIG. **18**), tether T40 (FIG. **19**), tether T41 (FIG. **20**) and tether T42 (FIG. **21**).

E. Examples of Synthetic Strategies for the Macrocyclic Compounds of the Invention

FIG. **22** presents a scheme depicting a thioester strategy for macrocyclic compounds of the present invention.

It should be noted that one or more of the amino acids indicated can be replaced by corresponding hydroxy acids and coupled to the next building block utilizing methods known to those in the art.

Example 47

Standard Procedure for Macrocyclization with Thioester Linker

The resin containing the cyclization precursor is combined in an appropriate vessel with pre-washed MP-carbonate resin [Argonaut Technologies, Foster City, Calif., commercially supplied MP-carbonate resin was treated with 3×THF (1 L per 400 g) and dried O/N at 30° C. in a vacuum oven] (1.4 to 1.6 eq relative to the initial loading of the synthesis resin). A 0.2 M DIPEA solution in THF was then added to the combined resins (1 mL/60 mg MP-carbonate resin) and the suspension agitated O/N at rt. Subsequently, the resin was filtered and rinsed 2×THF. The combined filtrates are collected together in an appropriate vessel, then the volatile contents evaporated under reduced pressure [in addition to the standard methods, solvent can also be removed in vacuo using centrifugal evaporation (ThermoSavant Discovery®, SpeedVac® or comparable) (Thermo Electron Corporation, Waltham, Mass.)] to provide the crude macrocycles.

Example 48

Standard Procedure for Silver-Assisted Macrocyclization with Thioester Linker

Except for the cyclization itself and subsequent work-up, this procedure is identical to that of Example 47. The resin containing the cyclization precursor was combined in an appropriate vessel with pre-washed MP-carbonate resin [Argonaut Technologies, commercially supplied MP-carbonate resin was treated with THF (3×, 1 L per 400 g) and dried O/N at 30° C. in a vacuum oven] (1.4 to 1.6 eq relative to the initial loading of the synthesis resin). To this was added THF (1 mL per 100 mg resin) and silver trifluoroacetate (1 eq relative to the initial loading of the resin). Finally, an amount of DIPEA sufficient to obtain a 0.2 M solution was added. The reaction mixture was agitated at rt O/N. The solution was then filtered and the resins washed 2×THF. The filtrates are collected together in an appropriate vessel, then evaporated under reduced pressure [(the volatile contents could also be removed in vacuo using centrifugal evaporation (ThermoSavant Discovery®, SpeedVace or comparable)] to provide the crude macrocycles. For this procedure, silver trifluoroacetate should be stored in a dessicator between uses. In addition, it is recommended to use a new bottle of THF (or a bottle that has been recently opened under N_2 or Ar) to minimize formation of silver oxide.

Additionally, a ring-closing metathesis (RCM) strategy, as developed by Grubbs et al. can also be used to access some of the macrocyclic compounds of the invention (see for example U.S. Pat. No. 5,811,515; Grubbs, R. H. et al. *J. Org. Chem.* 2001, 66, 5291-5300; Furstner, A. Angew. Chem. Int. Ed. 2000, 39, 3012-3043).

To access certain derivatives of compounds of the present invention, additional reactions from those in the general scheme were required. For some, it was advantageous to react the functionality to be derivatized prior to the formation of the macrocyclic ring. The cyclic structure can restrict access of reagents to that functionality. For example, in the synthesis of N-methyl and N-acyl derivatives of macrocycles, where the secondary nitrogen atom of the ring is the site of derivatization, the reaction is preferred to be performed prior to the application of the appropriate cyclization protocol.

In other cases, for example the derivatization of side chain functionality, the reaction was best performed after formation of the macrocyclic ring. For example, further reaction of amino moieties on side chains examples was typically efficiently done by reaction of the partially protected macrocycle. In this manner, acylation, sulfonylation, alkylation (via reductive amination), guanidine and urea formation were performed via standard methods.

Table 1, hereinbelow, shows a representative, but by no means exclusive, summary of the chemical synthesis of several representative compounds of the invention.

TABLE 1

Synthesis of Representative Compounds of the Present Invention

	AA_1	AA_2	AA_3	Tether	Tether Attachment	Additional Steps
1	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Nva	Ddz-T8	Example 29	none
2	Bts-D-Phe	Boc-D-Val	Boc-Nva	Boc-T8	Example 29	none
3	Bts-D-Phe	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
4	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Nva	Ddz-T9	Example 29	none
5	Bts-D-Tyr(tBu)	Boc-D-Ala	Boc-Nva	Ddz-T8	Example 29	none
6	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Met	Ddz-T8	Example 29	none
7	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Nle	Ddz-T8	Example 29	none
8	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Phe	Ddz-T8	Example 29	none
9	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Val	Ddz-T8	Example 29	none
10	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Leu	Ddz-T9	Example 29	none
11	Bts-D-2-Nal	Boc-D-Val	Boc-Nva	Boc-T8	Example 29	none
12	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Abu	Ddz-T8	Example 29	none
13	Bts-D-Phe	Boc-D-Val	Boc-Leu	Boc-T9	Example 29	none
14	Bts-D-2-Nal	Boc-D-Val	Boc-Leu	Boc-T9	Example 29	none
15	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
16	Bts-D-Phe(4Cl)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
17	Bts-D-Trp(Boc)	Boc-D-Val	Boc-Nva	Ddz-T9	Example 29	none
18	Bts-D-Tyr(tBu)	Boc-D-2-Abu	Boc-Nva	Ddz-T9	Example 29	none
19	Bts-D-Phe(4F)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
20	Bts-D-Phe	Boc-D-Val	Boc-Leu	Boc-T8	Example 29	none
21	Bts-D-2-Nal	Boc-D-Val	Boc-Leu	Boc-T8	Example 29	none
22	Bts-D-Tyr(OMe)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
23	Bts-D-1-Nal	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
24	Bts-D-2-Thi	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
25	Bts-D-Phe(2Cl)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
26	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Cpa	Ddz-T9	Example 29	none
27	Bts-D-4-Thz	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
28	Bts-D-3-Pal	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
29	Bts-D-Tyr(tBu)	Boc-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	none
30	Bts-D-Tyr(tBu)	Hnva(THP)	Boc-Nva	Ddz-T9	Example 29	none
34	Bts-D-Tyr(tBu)	Ddz-D-Tyr(tBu)	Boc-Nva	Ddz-T8	Example 29	None
38	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Ala	Ddz-T8	Example 29	none
39	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Ala	Ddz-T8	Example 29	none
40	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Gly	Ddz-T8	Example 29	none
41	Bts-D-Tyr(tBu)	Boc-DPhe	Boc-Nva	Ddz-T8	Example 29	none
52	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Phg	Ddz-T8	Example 29	none
55	Bts-D-Tyr(tBu)	Ddz-D-Val	Ddz-Lys(Boc)	Ddz-T8	Example 29	none
56	Bts-D-Tyr(tBu)	Ddz-D-Val	Ddz-Orn(Boc)	Ddz-T8	Example 29	none
57	Bts-D-Tyr(tBu)	Ddz-D-Val	Ddz-Ser(tBu)	Ddz-T8	Example 29	none

TABLE 1-continued

Synthesis of Representative Compounds of the Present Invention						
	AA_1	AA_2	AA_3	Tether	Tether Attachment	Additional Steps
58	Bts-D-Tyr(tBu)	Ddz-D-Val	Ddz-Tyr(tBu)	Ddz-T8	Example 29	none
59	Bts-D-Tyr(tBu)	Ddz--D-Val	Ddz-Trp(Boc)	Ddz-T8	Example 29	none
60	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Tyr(OMe)	Ddz-T8	Example 29	none
65	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Nva	Ddz-T2	Example 29	none
71	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Nva	Ddz-T10	Example 29	none
72	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-2-Nal	Ddz-T8	Example 29	none
76	Bts-D-Tyr(tBu)	Boc-D-2-Nal	Boc-Nva	Ddz-T8	Example 29	none
77	Bts-D-Tyr(tBu)	Boc-D-Nle	Boc-Nva	Ddz-T8	Example 29	none
80	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Ile	Ddz-T8	Example 29	none
85	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-D-Nva	Ddz-T8	Example 29	none
87	Bts-D-Bip	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
88	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Nva	Ddz-T9	Example 29	none
89	Bts-D-Hfe	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
90	Bts-D-Dip	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
91	Bts-D-Tyr(tBu)	Boc-D-Nva	Boc-Nva	Ddz-T9	Example 29	none
92	Bts-D-Tyr(tBu)	Boc-D-Tle	Boc-Nva	Ddz-T9	Example 29	none
96	Bts-D-Tyr(tBu)	Boc-β-Ala	Boc-Nva	Ddz-T9	Example 29	none
97	Bts-D-Tyr(tBu)	Boc-D-Chg	Boc-Nva	Ddz-T9	Example 29	none
98	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Nva	Ddz-T18	Example 29	none
99	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Nva	Ddz-T15	Example 29	none
109	Bts-D-Tyr(tBu)	Boc-D-Val	Ddz-Dab(Boc)	Ddz-T9	Example 29	none
110	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Nva	Ddz-T11	Example 29	none
111	Bts-D-Tyr(tBu)	Boc-D-Val	Hval(THP)	Ddz-T9	Example 29	none
112	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Nva	Ddz-T9	Example 29	none
120	Bts-D-Tyr(tBu)	Boc-D-Pro	Boc-Nva	Ddz-T8	Example 29	none
121	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Nva	Ac-T8-NH2	Example 29	none
122	Boc-D-3-Pal	Boc-D-Val	Boc-Nva	Boc-T9	Example 30	none
123	Boc-D-2-Pal	Boc-D-Val	Boc-Nva	Boc-T9	Example 30	none
124	Boc-D-4-Pal	Boc-D-Val	Boc-Nva	Boc-T9	Example 30	none
125	Bts-D-Tyr(tBu)	Boc-D-Cpg	Boc-Nva	Boc-T9	Example 29	none
126	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-NMeLeu	Boc-T9	Example 29	none
127	Boc-D-His(Mts)	Boc-D-Val	Boc-Nva	Boc-T12	Example 30	none
128	Bts-D-Tyr(OMe)	Boc-D-Val	Boc-Leu	Boc-T9	Example 29	none
129	Bts-D-1-Nal	Boc-D-Val	Boc-Leu	Boc-T9	Example 29	none
130	Bts-D-2-Thi	Boc-D-Val	Boc-Leu	Boc-T9	Example 29	none
131	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Leu	Boc-T9	Example 29	none
132	Bts-D-Phe(4Cl)	Boc-D-Val	Boc-Leu	Boc-T9	Example 29	none
133	Bts-D-Phe(4F)	Boc-D-Val	Boc-Leu	Boc-T9	Example 29	none
134	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Leu	Boc-T2	Example 29	none
135	Bts-D-Tyr(OMe)	Boc-D-Val	Boc-Leu	Boc-T11	Example 29	none

TABLE 1-continued

	Synthesis of Representative Compounds of the Present Invention					
	AA_1	AA_2	AA_3	Tether	Tether Attachment	Additional Steps
136	Bts-D-1Nal	Boc-D-Val	Boc-Leu	Boc-T11	Example 29	none
137	Bts-D-2-Thi	Boc-D-Val	Boc-Leu	Boc-T11	Example 29	none
138	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Leu	Boc-T11	Example 29	none
139	Bts-D-Phe(4Cl)	Boc-D-Val	Boc-Leu	Boc-T11	Example 29	none
140	Bts-D-Phe(4F)	Boc-D-Val	Boc-Leu	Boc-T11	Example 29	none
141	Bts-D-Tyr(OMe)	Boc-D-Val	Boc-Cpa	Boc-T9	Example 29	none
142	Bts-D-1-Nal	Boc-D-Val	Boc-Cpa	Boc-T9	Example 29	none
143	Bts-D-2-Thi	Boc-D-Val	Boc-Cpa	Boc-T9	Example 29	none
144	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Cpa	Boc-T9	Example 29	none
145	Bts-D-Phe(4Cl)	Boc-D-Val	Boc-Cpa	Boc-T9	Example 29	none
146	Bts-D-Phe(4F)	Boc-D-Val	Boc-Cpa	Boc-T9	Example 29	none
147	Bts-D-Tyr(OMe)	Boc-D-Val	Boc-Cpa	Boc-T11	Example 29	none
148	Bts-D-1-Nal	Boc-D-Val	Boc-Cpa	Boc-T11	Example 29	none
149	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Cpa	Boc-T11	Example 29	none
150	Bts-D-Phe(4Cl)	Boc-D-Val	Boc-Cpa	Boc-T11	Example 29	none
151	Bts-D-Phe(4F)	Boc-D-Val	Boc-Cpa	Boc-T11	Example 29	none
152	Bts-D-Tyr(OMe)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	none
153	Bts-D-1-Nal	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	none
154	Bts-D-2-Thi	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	none
155	Bts-D-Phe(3Cl)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	none
156	Bts-D-Phe(4Cl)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	none
157	Bts-D-Phe(4F)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	none
158	Bts-D-Phe(3Cl)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T11	Example 29	none
159	Bts-D-Tyr(But)	Boc-D-Ile	Boc-Nva	Boc-T9	Example 29	none
160	Bts-D-Tyr(But)	Boc-D-allolle	Boc-Nva	Boc-T9	Example 29	none
161	Boc-D-Phe(4CH2NHFmoc)	Boc-D-Val	Boc-Nva	Boc-T9	Example 30	none
162	Bts-D-Phe(2Me)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
163	Bts-D-Phe(3Me)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
164	Bts-D-Phe(4Me)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
165	Bts-D-Phe(3OMe)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
166	Bts-D-Phe(2OMe)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
167	Bts-D-3-benzothienyl	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
168	Bts-D-3-Thi	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
169	Bts-D-HomoPhe(3Cl)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
170	Bts-D-Phe(3,4diCl)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
171	Bts-D-Phe(3,4diF)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
172	Bts-D-Phe(3,4diOMe)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
173	Bts-D-1Nal	Hnva(THP)	Boc-Nva	Boc-T9	Example 29	none
174	Bts-D-Tyr(OMe)	Hnva(THP)	Boc-Nva	Boc-T9	Example 29	none
175	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Nva	Boc-T33b	Example 29	none
176	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Nva	Boc-T33a	Example 29	none
177	Bts-D-Tyr(tBu)	Boc-D-Val	Boc-Nva	Boc-T28	Example 29	none

TABLE 1-continued

	Synthesis of Representative Compounds of the Present Invention					
	AA_1	AA_2	AA_3	Tether	Tether Attachment	Additional Steps
178	Bts-D-Tyr(OMe)	Ddz-D-Val	Ddz-Ser(tBu)	Ddz-T9	Example 29	none
179	Bts-D-1-Nal	Ddz-D-Val	Ddz-Ser(tBu)	Ddz-T9	Example 29	none
180	Bts-D-2-Thi	Ddz-D-Val	Ddz-Ser(tBu)	Ddz-T9	Example 29	none
181	Bts-D-Phe(3Cl)	Ddz-D-Val	Ddz-Ser(tBu)	Ddz-T9	Example 29	none
182	Bts-D-Phe(4Cl)	Ddz-D-Val	Ddz-Ser(tBu)	Ddz-T9	Example 29	none
183	Bts-D-Phe(4F)	Ddz-D-Val	Ddz-Ser(tBu)	Ddz-T9	Example 29	none
184	Bts-D-1-Nal	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T11	Example 29	none
185	Bts-D-Phe(4Cl)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T11	Example 29	none
186	Ddz-D-Tyr(tBu)	Ddz-D-Val	Ddz-His(Mts)	Ddz-T9	Example 30	none
187	Bts-D-Phe(3CF3)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
188	Bts-D-Phe(3F)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
189	Bts-D-Phe(4NO2)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
190	Bts-D-3-benzothienyl	Boc-D-Val	Boc-Cpa	Boc-T9	Example 29	none
191	Bts-D-Phe(3OMe)	Boc-D-Val	Boc-Cpa	Boc-T9	Example 29	none
192	Bts-D-Phe(3,4diCl)	Boc-D-Val	Boc-Cpa	Boc-T9	Example 29	none
193	Bts-D-Phe(3,4diF)	Boc-D-Val	Boc-Cpa	Boc-T9	Example 29	none
194	Bts-D-Tyr(OMe)	Boc-D-Val	Boc-Nva	Boc-T34	Example 29	none
195	Bts-D-Tyr(OMe)	Boc-D-Val	Boc-Nva	Boc-T38	Example 29	none
196	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Cpa	Ddz-T32(Boc)	Example 29	none
197	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Cpa	Boc-T34	Example 29	none
198	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Cpa	Boc-T38	Example 29	none
199	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Cpa	Boc-T41	Example 29	none
200	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Cpa	Boc-T8	Example 29	none
201	Bts-D-1-Nal	Boc-D-Val	Boc-Nva	Boc-T8	Example 29	none
202	Bts-D-Phe(3OMe)	Boc-D-Val	Boc-Nva	Boc-T8	Example 29	none
203	Bts-D-Phe(4Cl)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	acetylation
204	Bts-D-Phe(4Cl)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	guanidinylation
205	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-NMeLeu	Boc-T9	Example 29	none
206	Bts-D-Phe(4Cl)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	mesylation
207	Bts-D-Phe(4Cl)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	TMS-isocyanate followed by dilute acid
208	Bts-D-Tyr(tBu)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	guanidinylation
209	Bts-D-Tyr(tBu)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	acetylation
210	Bts-D-Tyr(tBu)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	reductive amination with acetone
211	Bts-D-Phe(4Cl)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	reductive amination with excess formaldehyde
212	Bts-D-Phe(4Cl)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	reductive amination with acetone
213	Bts-D-Tyr(3,5dil)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none

TABLE 1-continued

Synthesis of Representative Compounds of the Present Invention

	AA_1	AA_2	AA_3	Tether	Tether Attachment	Additional Steps
214	Bts-D-Tyr(OMe)	Boc-D-Val	Boc-Hse(Bzl)	Boc-T9	Example 29	hydrogenolysis for protecting group removal
215	Bts-D-Tyr(tBu)	Ddz-D-Val	Ddz-Dap(Boc)	Ddz-T9	Example 29	reductive amination with excess formaldehyde
216	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Cpa	Boc-T40	Example 29	none
217	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Cpa	Boc-T36	Example 29	none
218	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Nva	Boc-T39	Example 29	none
219	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Nva	Boc-T37	Example 29	none
220	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Nva	Boc-T39	Example 29	none
221	Bts-D-Phe(3Cl)	Boc-D-Val	Boc-Nva	Boc-T35	Example 29	none
222	Bts-D-Tyr(3tBu)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	none
223	Bts-D-Tyr(But)	Boc-D-Val	Boc-Nva	Boc-T9	Example 29	acetylation
224	Bts-D-1-Nal	Boc-D-Val	Boc-Leu	Boc-T9	Example 29	reductive amination with formaldehyde
225	Bts-D-1-Nal	Boc-D-Val	Boc-Leu	Boc-T9	Example 29	acetylation
226	Bts-D-1-Nal	Boc-D-Val	Boc-Leu	Boc-T9	Example 29	reductive amination with aldehyde
227	Bts-D-1-Nal	Boc-D-Val	Boc-Leu	Boc-T9	Example 29	reductive amination with benzaldehyde

Notes
Any amino acid or tether designated as the Boc derivative could be substituted with the corresponding Ddz derivative.

D. Analytical Data for Selected Compounds of the Invention

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer (Varian, Inc., Palo Alto, Calif.) and are referenced internally with respect to the residual proton signals of the solvent. Information about the conformation of the molecules in solution can be determined utilizing appropriate two-dimensional NMR techniques known to those skilled in the art. HPLC purifications were run on a Waters Xterra® MS C18 column, using the Waters FractionLynx® system (Waters Corporation, Milford, Mass.). Automated medium pressure chromatographic purifications were performed on an Isco CombiFlash® 16× system with disposable silica or C18 cartridges that permitted up to sixteen (16) samples to be run simultaneously (Teledyne Isco, Inc., Lincoln, Nebr.). MS spectra were recorded on a Waters Micromass® Platform II or ZQ™ system. HRMS spectra were recorded with a VG Micromass ZAB-ZF spectrometer. Chemical and biological information were stored and analyzed utilizing the ActivityBase® database software (ID Business Solutions Ltd., Guildford, Surrey, UK).

General Methods for Analytical HPLC Analyses

HPLC analyses are performed on a Waters Alliance® system 2695 running at 1 mL/min using an Xterra MS C18 column 4.6×50 mm (3.5 μm). A Waters 996 PDA provided UV data for purity assessment (Waters Corporation, Milford, Mass.). An LCPackings (Dionex Corporation, Sunnyvale, Calif.) splitter (50:40:10) allowed the flow to be separated in three parts. The first part (50%) went to a Micromass® Platform II MS equipped with an APCI probe for identity confirmation. The second part (40%) went to an evaporative light scattering detector (ELSD, Polymer Laboratories, now part of Varian, Inc., Palo Alto, Calif., PL-ELS-1000™) for purity assessment and the last portion (10%) to a chemiluminescence nitrogen detector (CLND, Antek® Model 8060, Antek Instruments, Houston, Tex., part of Roper Industries, Inc., Duluth, Ga.) for quantitation and purity assessment. Data was captured and processed utilizing the most recent version of the Waters Millenium® software package (Milford, Mass.).

An example LC method suitable for compounds of the present invention uses MeOH as solvent A, H_2O as solvent B and 1% TFA/H_2O as solvent D. Initial mobile-phase composition is 5% A, 85% B and 10% D. Details of the standard gradient method are shown below:

Time	A %	B %	D %	Curve
0.00	5	85	10	6
1.00	5	85	10	6
6.00	50	40	10	6
9.00	50	40	10	6
14.00	90	0	10	6
17.00	90	0	10	6
17.50	5	85	10	6
20.00	5	85	10	6

Compounds 2-6, 8-10, 56, 65 and 144 are as defined in Table (3), hereinbelow.

Compound 2

Yield: 12 mg pure macrocycle was obtained (CLND quantification).

^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.83 (m, 1H); 8.53 (m, 1H); 7.63 (m, 1H); 7.4-7.08 (m, 7H); 7.00-6.84 (m, 2H); 6.60 (d, 15 Hz, 1H); 6.41 (dt, 15 Hz, 5.4 Hz, 1H); 4.35 (m, 1H); 4.25-4.05 (m, 3H); 3.94 (dt, 1H, 6 Hz, 15 Hz); 3.79 (dd, 1H, 3.6 Hz, 8.4 Hz); 3.60 (m, 1H); 3.52-3.40 (bd, 1H); 3.22-3.06 (m, 4H); 1.88 (m, 2H); 1.54-1.28 (m, 2H); 1.25 (d, 3H, 4.8 Hz); 1.22 (d, 3H, 2.7 Hz); 0.92-0.80 (m, 6H).

HRMS calc. for $C_{30}H_{40}N_4O_4$: 520.3049. found 520.3057±0.0016.

HPLC [standard gradient method (refers to that presented in General Methods for Analytical HPLC Analyses)] t_R=9.55 min.

Compound 4

Yield: 12 mg pure macrocycle was obtained (CLND quantification).

^{1}H NMR (300 MHz, DMSO-d$_6$) δ 9.35 (b, 1H); 8.98 (b, 1H); 5.52 (d, 1H, 8.4 Hz); 8.38 (b, 1H); 7.25 (b, 1H); 7.13-7.07 (m, 4H); 6.86 (t, 2H, 7.5 Hz); 6.57 (d, 2H, 8.7 Hz); 4.33 (b, 1H); 4.21-4.02 (m, 3H); 3.78 (dd, 1H, 3.3 Hz; 8.1 Hz); 3.65-3.54 (m, 1H); 3.31-3.23 (m, 1H); 3.13-3.02 (m, 4H); 2.78-2.2.28-2.18 (m, 1H); 2.0-1.80 (m, 2H); 1.50-1.30 (m, 3H); 1.25 (d, 3H, 4.5 Hz); 1.22 (d, 3H, 4.5 Hz); 1.01 (d, 3H, 6.6 Hz); 0.90 (d, 3H, 6.6 Hz); (t, 3H, 7.5 Hz).

^{13}C NMR (75.5 MHz, DMSO-d$_6$) δ 172.22; 171.37; 157.77; 157.44; 156.04; 131.76; 130.80; 130.70; 127.88; 121.82; 115.83; 111.71; 62.13; 60.62; 54.21; 52.81; 47.13; 42.47; 33.31; 29.69; 29.30; 28.61; 20.36; 19.44; 18.72; 17.60; 13.97.

HRMS calc. for $C_{30}H_{42}N_4O_5$: 538.3155. found: 538.3145±0.0016.

HPLC (standard gradient) t_R=8.12 min.

Compound 5

Yield: 17 mg pure macrocycle was obtained (CLND quantification).

^{1}H NMR (300 MHz, DMSO-d$_6$) δ 9.02 (b, 1H); 8.47 (d, 1H, 8.4 Hz); 7.7 (b, 1H); 7.58 (d, 1H, 5.4 Hz); 7.28 (dd, 1H, 7.8 Hz, 0.8 Hz); 7.20 (t, 1H, 9.0 Hz, 0.8 Hz); 7.14 (d, 2H, 8.4 Hz); 6.98-6.91 (m, 3H); 6.66 (d, 8.7 Hz); 6.63 (d, 1H, 15.0 Hz); 6.43 (dt, 1H, 6.0 Hz, 15.0 Hz); 4.28-3.86 (m, 6H); 3.60-3.40 (m, 2H); 3.22-3.12 (m, 1H0; 3.05 (d, 2H, 5.4 Hz); 1.92-1.80 (m, 1H); 1.56-1.40 (m, 1H); 1.36-1.20 (m, 2H); 1.25 (d, 3H, 6.6 Hz); 0.84 (t, 3H, 7.2 Hz).

^{13}C NMR (75.5 MHz, DMSO-d$_6$) δ 172.54; 171.86; 158.97; 158.56; 127.39; 155.84; 131.62; 129.73; 129.20; 129.02; 128.43; 126.30; 124.51; 122.01; 115.85; 112.88; 61.23; 52.90; 51.23; 47.08; 42.66; 36.13; 33.30; 21.14; 19.57; 17.07; 14.14; 11.49.

HRMS calc. for $C_{28}H_{36}N_4O_5$: 508.2685. found: 508.2681±0.0015.

HPLC (standard gradient) t_R=7.67 min.

Compound 6

Yield: 16 mg pure macrocycle was obtained (CLND quantification).

^{1}H NMR (300 MHz, DMSO-d$_6$) δ 9.37 (b, 1H); 8.87 (b, 1H); 8.61 (d, 1H, 8.7 Hz); 7.62 (b, 1H); 7.27 (d, 1H, 7.8 Hz); 7.21 (t, 1H, 8.4 Hz); 7.14 (d, 2H, 8.4 Hz); 6.98-6.87 (m, 3H); 6.64 (d, 2H, 8.1 Hz); 6.70 (d, 1H, 15.6 Hz); 6.39 (dt, 1H, 6.3 Hz, 15.6 Hz); 4.44-4.36 (m, 1H); 4.34-4.08 (m, 2 Hz); 4.45-3.92 (dt, 1H, 6.9 Hz, 15.6 Hz); 3.74 (dd, 1H, 3.6 Hz, 8.4 Hz); 3.54-3.26 (m, 3H); 3.22-3.02 (m, 3H); 2.60-2.36 (m, 4H); 2.24-2.14 (m, 1H); 2.02 (s, 3H); 1.96-1.89 (m, 1H); 1.80-1.66 (m, 1H); 1.01 (d, 3H, 6.3 Hz); 0.90 (d, 3H, 6.6 Hz).

^{13}C NMR (75.5 MHz, DMSO-d$_6$) δ 171.51; 171.26; 158.90; 158.49; 157.38; 155.86; 131.63; 129.82; 129.21; 128.86; 128.63; 126.21; 121.98; 115.83; 112.83; 62.11; 61.06; 51.97; 47.10; 42.78; 30.91; 30.67; 29.34; 20.37; 19.39; 15.06.

HRMS calc. for $C_{30}H_{40}N_4O_5S$: 568.2719. found: 568.2711±0.0017.

HPLC R_t (general method) 7.92 min.

Compound 8

Yield: 27 mg pure macrocycle was obtained (CLND quantification).

^{1}H NMR (300 MHz, DMSO-d$_6$) δ 9.05 (b, 1H); 8.43 (b, 1H); 8.34 (d, 1H, 9.3 Hz); 7.40 (b, 1H); 6.97 (d, 1H, 7.5 Hz); 6.92-6.74 (m, 9H); 6.67-6.54 (m, 2H); 6.33-6.25 (m, 3H); 6.10 (dt, 1H, 5.7 Hz, 16.2 Hz); 4.22 (dt, 1H, 0.9 Hz, 12 Hz); 3.94-6.66 (m, 4H); 3.30 (dd, 1H, 3.6 Hz, 7.8 Hz); 3.24 (m, 1H); 3.18 (m, 1H); 2.85-2.68 (m, 3H); 2.44-2.23 (m, 2H); 1.32 (o, 1H, 7.5 Hz); 0.97-0.89 (m, 1H); 0.42 (d, 3H, 6.6 Hz); 0.01 (d, 3H, 6.6 Hz). ^{13}C NMR (75.5 MHz, DMSO-d$_6$) δ 171.20; 157.35; 155.88; 139.12; 131.61; 130.87; 129.74; 129.21; 128.77; 128.88; 126.85; 126.19; 121.97; 115.82; 112.84; 62.04; 61.10; 55.07; 50.01; 47.09; 42.85; 37.42; 29.11.

HRMS calc. For $C_{34}H_{42}N_4O_5$: 586.3155. found: 586.3145±0.0017.

HPLC R_t (general method) 9.34 min.

Compound 9

Yield: 17 mg pure macrocycle was obtained (CLND quantification).

^{1}H NMR (300 MHz, DMSO-d$_6$) δ 9.39 (b, 1H); 8.83 (b, 1H); 8.29 (d, 1H, 9.3 Hz); 7.62 (b, 1H); 7.28 (d, 1H, 6.6 Hz); 7.20 (t, 1H, 6.9 Hz); 7.12 (d, 2H, 7.8 Hz); 6.98-6.91 (m, 2H); 6.63 (d, 2H, 8.4 Hz); 6.58 (d, 1H, 16.2 Hz); 6.40 (dt, 1H, 5.7 Hz, 16.2 Hz); 4.29-4.13 (m, 3H); 4.03-3.92 (m, 2H); 3.52 (m, 1H); 3.15-3.05 (m, 3H); 2.45-2.37 (m, 1H);

1.96-1.88 (m, 1H); 1.25 (dd, 2H, 4.5 Hz; 6 Hz); 1.01 (d, 3H, 6.3 Hz); 0.91 (d, 3H, 6.6 Hz); 0.86 (d, 3H, 7.2 Hz); 0.81 (d, 3H, 6.6 Hz).

^{13}C NMR (75.5 MHz, DMSO-d$_6$) δ 171.85; 171.17; 157.37; 155.87; 131.59; 129.88; 129.18; 128.97; 128.78; 128.51; 126.16; 121.97; 115.83; 112.85; 61.55; 61.18; 58.15; 54.22; 47.08; 42.89; 36.32; 29.35; 29.00; 20.34; 19.56; 18.73; 17.44.

HRMS calc. for $C_{30}H_{40}N_4O_5$ 536.2998. found: 536.2990±0.0017.

HPLC (standard gradient) t_R=8.15 min.

Compound 10

Yield: 24 mg pure macrocycle was obtained (CLND quantification).

^{1}H NMR (300 MHz, DMSO-d$_6$) δ 9.33 (b, 1H); 8.82 (b, 1H); 8.56 (d, 1H, 8.3 Hz); 7.60 (b, 1H); 7.27 (d, 2H, 7.8 Hz); 7.20 (t, 1H, 7.8 Hz); 7.13 (d, 2H, 8.4 Hz); 6.95 (t, 2H, 7.8 Hz); 6.64 (d, 2H, 8.4 Hz); 6.57 (d, 1H, 15.4 Hz); 6.38 (dt, 1H, 15.4 Hz, 5.8 Hz); 4.26-4.10 (m, 3H); 3.96 (dt, 1H, 5.4 Hz, 8.4 Hz); 3.77 (dd, 1H, 3.7 Hz, 7.8 Hz); 3.51-3.24 (m, 3H); 3.18-3.02 (m, 3H); 1.90 (h, 1H, 6.4 Hz); 1.73-1.54 (m, 2H); 1.45 (dt, 1H, 6.7 Hz, 0.9 Hz); 0.99 (d, 3H, 6.6 Hz); 0.89 (d, 3H, 6.3 Hz); 0.87 (d, 3H, 6.0 Hz); 0.80 (d, 3H, 6.3 Hz).

^{13}C NMR (75.5 MHz, DMSO-d$_6$) δ 172.23; 171.17; 157.37; 155.88; 131.62; 129.82; 129.19; 128.95; 128.59; 126.24; 121.99; 115.84; 112.88; 64.23; 61.98; 61.14; 51.43; 61.14; 51.43; 47.07; 42.81; 29.38; 24.85; 24.11; 21.00; 20.32; 19.30.

HRMS calc. for $C_{31}H_{42}N_4O_5$ 550.3155. found: 550.3150±0.0016.

HPLC (standard gradient) t_R=8.91 min.

Compound 56

Yield: 16 mg pure macrocycle was obtained (CLND quantification).

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.39 (b, 1H); 8.90 (b, 1H); 8.67 (d, 1H, 8.4 Hz); 7.74 (b, 4H); 7.29-7.08 (m, 4H); 6.99-6.87 (m, 2H); 6.64 (d, 2H, 8.1 Hz); 6.61 (d, 1H, 16.5 Hz); 6.40 (dt, 1H, 5.7 Hz, 16.5 Hz); 4.40-4.06 (m, 4H); 4.02-3.95 (m, 1H); 3.79 (dd, 1H, 3.6 Hz, 7.8 Hz); 3.55-3.30 (m, 2H); 3.16-3.05 (m, 3H); 2.82-2.69 (m, 2H); 2.02-1.85 (m, 2H); 1.64-1.43 (m, 3H); 1.29-1.23 (m, 1H); 1.01 (d, 3H, 6.3 Hz); 0.91 (d, 3H, 6.3 Hz); 0.86-0.84 (m, 2H).

HPLC (standard gradient) t_R=5.71 min.

Compound 65

Yield: 17 mg pure macrocycle was obtained (CLND quantification).

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (b, 1H); 9.39 (b, 1H); 8.88 (b, 1H); 8.70 (d, 1H, 7.5 Hz); 8.57 (d, 1H, 4.2 Hz); 7.27 (t, 6 Hz); 6.96 (d, 2H, 8.4 Hz); 6.66 (d, 2H, 8.4 Hz); 5.78-5.68 (m, 1H); 5.42-5.33 (m, 1H); 3.96-3.89 (m, 1H); 3.80-3.57 (m, 5H); 3.41-3.34 (m, 1H); 3.10-2.90 (m, 1H); 2.78-2.66 (m, 1H); 2.21-2.10 (m, 1H); 2.06-1.93 (m, 1H); 1.70-1.60 (m, 1H); 1.52-1.41 (m, 1H); 1.39-1.26 (m, 1H); 1.25 (d, 3H, 4.8 Hz); 1.23 (d, 3H, 4.5 Hz); 0.83 (dd, 3H, 3 Hz, 4.5 Hz).

^{13}C NMR (75.5 MHz, DMSO-d_6) δ 172.68; 172.63; 159.15; 158.73; 157.38; 157.25; 130.89; 124.99; 116.03; 62.51; 62.12; 54.29; 49.27; 42.47; 32.77; 30.43; 28.85; 20.46; 19.59; 18.72; 17.39; 13.90; 13.09.

HRMS calc. for $C_{24}H_{36}N_4O_4$: 444.2736. found: 444.2726±0.0013.

HPLC (standard gradient) t_R=6.80 min.

Compound 144

^{1}H NMR (300 MHz, CD_3OD) δ 7.4 (m, 1H); 7.27 (dt, 1H, 1.5 Hz, 6.6 Hz); 7.22-7.14 (m, 2H); 7.08-6.98 (m, 2H); 6.78 9t, 2H, 6.6 Hz); 4.45-4.39 (m, 2H); 4.15 (d, 2H, 8.1 Hz); 7.74 (d, 1H, 9.3 Hz); 3.54 (d, 1H, 10.8 Hz); 3.35-3.22 (m, 2H); 3.20 (q, 1H, 1.5 Hz); 2.82-2.71 (m, 1H); 2.61-2.55 (m, 1H); 2.21-2.11 (m, 1h); 2.02-1.94 (m, 1H); 1.74-1.40 (m, 5H); 1.04 (d, 3H, 6.6 Hz); 0.93 (d, 3H, 6.6 Hz); 0.74-0.64 9m, 1H); 0.45-0.28 (m, 2H); 0.15-0.08 (m, 1H); 0.06-0.02 (m, 1H).

^{13}C NMR (75.5 MHz, CD_3OD) δ 173.29; 172.14; 167.51; 155.47; 134.86; 134.81; 130.38; 130.31; 128.81; 128.25; 127.44; 121.63; 110.39; 107.71; 105.02; 67.10; 66.66; 62.81; 62.06; 60.10; 53.99; 41.44; 36.07; 31.91; 30.01; 29.18; 28.94; 27.79; 23.68; 23.15; 19.08; 18.25; 8.17; 4.98; 3.16.

HRMS: calc. for $C_{31}H_{41}N_4O_4C1568.2816$. found 568.2802±0.0017.

F. Mass Spectral Data for Selected Compounds of the Invention

TABLE 2

Analysis of selected compounds of the invention

	Molecular Formula	Molecular Weight (calculated)	Monoisotopic Mass	M + H Found
1	C30H40N4O5	536.7	536	537
2	C30H40N4O4	520.7	520	521
3	C30H42N4O4	522.7	522	523
4	C30H42N4O5	538.7	538	539
5	C28H36N4O5	508.6	508	509
6	C30H40N4O5S	568.7	568	569
7	C31H42N4O5	550.7	550	551
8	C34H42N4O5	586.7	586	587
9	C30H40N4O5	536.7	536	537
10	C31H42N4O5	550.7	550	551

TABLE 2-continued

Analysis of selected compounds of the invention

	Molecular Formula	Molecular Weight (calculated)	Monoisotopic Mass	M + H Found
11	C34H44N4O4	572.7	572	573
12	C29H38N4O5	522.6	522	523
13	C31H44N4O4	536.7	536	537
14	C35H46N4O4	586.8	586	587
15	C30H41N4O4Cl	557.1	556	557
16	C30H41N4O4Cl	557.1	556	557
17	C32H43N5O4	561.7	561	562
18	C29H40N4O5	524.7	524	525
19	C30H41N4O4F	540.7	540	541
20	C31H42N4O4	534.7	534	535
21	C35H44N4O4	584.7	584	585
22	C31H44N4O5	552.7	552	553
23	C34H44N4O4	572.7	572	573
24	C28H40N4O4S	528.7	528	529
25	C30H41N4O4Cl	557.1	556	557
26	C31H42N4O5	550.7	550	551
27	C27H39N5O4S	529.7	529	530
28	C29H41N5O4	523.7	523	524
29	C28H39N5O5	525.6	525	526
30	C30H41N3O6	539.7	539	540
34	C34H40N4O6	600.7	600	601
38	C28H36N4O5	508.6	508	509
39	C28H36N4O5	508.6	508	509
40	C27H34N4O5	494.6	494	495
41	C34H40N4O5	584.7	584	585
52	C33H38N4O5	570.7	570	571
55	C31H43N5O5	565.7	565	566
56	C30H41N5O5	551.7	551	552
57	C28H36N4O6	524.6	524	525
58	C34H40N4O6	600.7	600	601
59	C36H41N5O5	623.7	623	624
60	C35H42N4O6	614.7	614	615
65	C24H36N4O4	444.6	444	445
71	C29H40N4O6	540.7	540	541
72	C38H42N4O5	634.8	634	635
76	C38H42N4O5	634.8	634	635
77	C31H42N4O5	550.7	550	551
80	C31H42N4O5	550.7	550	551
85	C30H40N4O5	536.7	536	537
87	C36H46N4O4	598.8	598	599
88	C34H50N4O5	594.8	594	595
89	C31H44N4O4	536.7	536	537
90	C36H46N4O4	598.8	598	599
91	C30H42N4O5	538.7	538	539
92	C31H44N4O5	552.7	552	553
96	C28H38N4O5	510.6	510	511
97	C33H46N4O5	578.7	578	579
98	C24H39N5O4	461.6	461	462
99	C24H39N5O4	461.6	461	462
109	C29H41N5O5	539.7	539	540
110	C29H41N5O5	539.7	539	540
111	C30H41N3O6	539.7	539	540
112	C31H44N4O5	552.7	552	553
120	C30H38N4O5	534.6	534	535
121	C32H45N5O6	595.7	595	596
122	C31H43N4O4Cl	571.2	570	571
123	C29H41N5O4	523.7	523	524
124	C29H41N5O4	523.7	523	524
125	C30H40N4O5	536.7	536	537
126	C32H46N4O5	566.7	566	567
127	C30H38N6O3S	562.7	562	563
128	C32H46N4O5	566.7	566	567
129	C35H46N4O4	586.8	586	587
130	C29H42N4O4S	542.7	542	543
131	C31H43N4O4Cl	571.2	570	571
132	C31H43N4O4Cl	571.2	570	571
133	C31H43N4O4F	554.7	554	555
134	C25H37N4O3Cl	477.0	476	477
135	C31H45N5O5	567.7	567	568
136	C34H45N5O4	587.8	587	588
137	C28H41N5O4S	543.7	543	544
138	C30H42N5O4Cl	572.1	571	572
139	C30H42N5O4Cl	572.1	571	572
140	C30H42N5O4F	555.7	555	556
141	C32H44N4O5	564.7	564	565

TABLE 2-continued

Analysis of selected compounds of the invention

	Molecular Formula	Molecular Weight (calculated)	Monoisotopic Mass	M + H Found
142	C35H44N4O4	584.7	584	585
143	C29H40N4O4S	540.7	540	541
144	C31H41N4O4Cl	569.1	568	569
145	C31H41N4O4Cl	569.1	568	569
146	C31H41N4O4F	552.7	552	553
147	C31H43N5O5	565.7	565	566
148	C34H43N5O4	585.7	585	586
149	C30H40N5O4Cl	570.1	569	570
150	C30H40N5O4Cl	570.1	569	570
151	C30H40N5O4F	553.7	553	554
152	C29H41N5O5	539.7	539	540
153	C32H41N5O4	559.7	559	560
154	C26H37N5O4S	515.7	515	516
155	C28H38N5O4Cl	544.1	543	544
156	C28H38N5O4Cl	544.1	543	544
157	C28H38N5O4F	527.6	527	528
158	C27H37N6O4Cl	545.1	544	545
159	C31H44N4O5	552.7	552	553
160	C31H44N4O5	552.7	552	553
161	C31H45N5O4	551.7	551	552
162	C31H44N4O4	536.7	536	537
163	C31H44N4O4	536.7	536	537
164	C31H44N4O4	536.7	536	537
165	C31H44N4O5	552.7	552	553
166	C31H44N4O5	552.7	552	553
167	C32H42N4O4S	578.8	578	579
168	C28H40N4O4S	528.7	528	529
169	C31H43N4O4Cl	571.2	570	571
170	C30H40N4O4Cl2	591.6	590	591
171	C30H40N4O4F2	558.7	558	559
172	C32H46N4O6	582.7	582	583
173	C34H43N3O5	573.7	573	574
174	C31H43N3O6	553.7	553	554
175	C31H44N4O5	552.7	552	553
176	C31H44N4O5	552.7	552	553
177	C29H40N4O5	524.7	524	525
178	C29H40N4O6	540.7	540	541
179	C32H40N4O5	560.7	560	561
180	C26H36N4O5S	516.7	516	517
181	C28H37N4O5Cl	545.1	544	545
182	C28H37N4O5Cl	545.1	544	545
183	C28H37N4O5F	528.6	528	529
184	C31H40N6O4	560.7	560	561
185	C27H37N6O4Cl	545.1	544	545
186	C31H40N6O5	576.7	576	577
187	C31H41N4O4F3	590.7	590	591
188	C30H41N4O4F	540.7	540	541
189	C30H41N5O6	567.7	567	568
190	C33H42N4O4S	590.8	590	591
191	C32H44N4O5	564.7	564	565
192	C31H40N4O4Cl2	603.6	602	603
193	C31H40N4O4F2	570.7	570	571
194	C32H48N6O6	612.8	612	613
195	C32H46N4O5	566.7	566	567
196	C32H43N6O4Cl	611.2	610	611
197	C32H45N6O5Cl	629.2	628	629
198	C32H43N4O4Cl	583.2	582	583
199	C27H39N4O6Cl	551.1	550	551
200	C31H39N4O4Cl	567.1	566	567
201	C34H42N4O4	570.7	570	571
202	C31H42N4O5	550.7	550	551
203	C30H40N5O5Cl	586.1	585	586
204	C29H40N7O4Cl	586.1	585	586
205	C32H45N4O4Cl	585.2	584	585
206	C29H40N5O6SCl	622.2	621	622
207	C29H39N6O5Cl	587.1	586	587
208	C29H41N7O5	567.7	567	568
209	C30H41N5O6	567.7	567	568
210	C31H45N5O5	567.7	567	568
211	C30H42N5O4Cl	572.1	571	572
212	C31H44N5O4Cl	586.2	585	586
213	C30H40N4O5I2	790.5	790	791
214	C30H42N4O6	554.7	554	555
215	C30H43N5O5	553.7	553	554
216	C32H43N4O4Cl	583.2	582	583
217	C31H40N4O4FCl	587.1	586	587
218	C31H43N4O4Cl	571.2	570	571
219	C30H40N4O4Cl2	591.6	590	591
220	C31H43N4O4F	554.7	554	555
221	C30H40N4O4FCl	575.1	574	575
222	C34H50N4O5	594.8	594	595
223	C32H44N4O6	580.7	580	581
224	C36H48N4O4	600.8	600	601
225	C37H48N4O5	628.8	628	629
226	C39H49N5O4S	683.9	683	684
227	C42H52N4O4	676.9	676	677

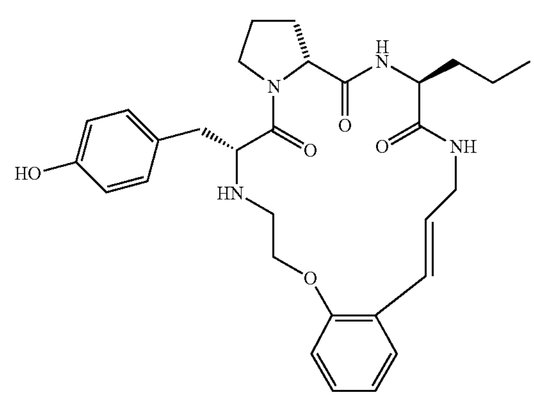
Notes
1. Molecular formulas and molecular weights (MW) are calculated automatically from the structure via ActivityBase ® software (IDBS, Guildford, Surrey, UK) or, for MW only, from the freeware program Molecular Weight Calculator v. 6.32
2. M + H obtained from LC-MS analysis using the General Method as described
3. All analyses conducted on material after preparative HPLC purification

Biological Methods and Results

The compounds of the present invention were evaluated for their ability to interact at the human motilin receptor utilizing a competitive radioligand binding assay as described in Method B1. Further characterization of the interaction can be performed utilizing the functional assays described in Methods B2, B3 and B4. Some of these methods can be conducted, if so desired, in a high throughput manner to permit the simultaneous evaluation of many compounds. Other assays have also been described that are suitable for HTS, such as that based upon the stable expression of a synthetic gene for the human motilin receptor.

Results for the examination of representative compounds of the present invention using Method B1 are presented in Table 3. The binding activity is listed as ranges with the following levels: A=0.001-0.10 μM; B=0.10-1.0 μM; C=1.0-10.0 μM. In addition, the assay results of two additional compounds using this Method are shown below. As can be observed, this demonstrates the activity of a representative bicyclic compound of Formula IV of the invention, which resulted from incorporation of D-proline as the second recognition building block. Significantly, the lack of binding activity obtained with compound 121, which is the linear analogue of compound 1 (K_i=level B), illustrates the critical importance of the cyclic structure to attaining the desired interaction.

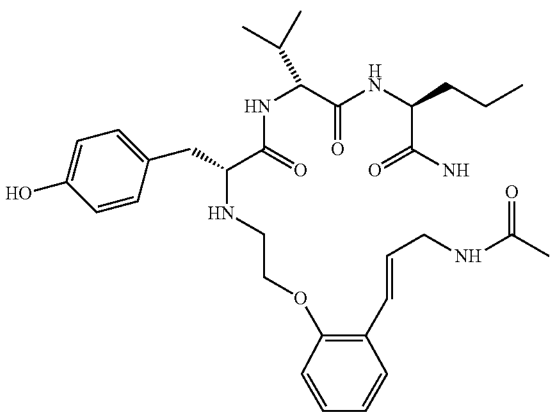
Compound 120



K_i = level B

-continued

Compound 121



K_i > 10 μM

Competitive binding curves for two representative compounds of the invention (Compounds 8 and 11) are presented in FIG. **23** and FIG. **24**, respectively.

For determination of functional significance of the binding, the compounds are preferably tested in the Aequorin assay as described in Method B2, although the procedure of Method B3 is also applicable. As can be seen from the data presented in Table 4, the representative compounds examined act as antagonists at the motilin receptor and are devoid of agonist activity at the concentrations studied. The functional activity is listed as ranges with the following levels: A=0.001-0.10 μM; B=0.10-1.0 μM. The higher sensitivity of the assay of Method B2, almost 100 times that of Method C, makes it the preferred one for this assessment. This is evident in the EC_{50} values obtained in each for the positive agonist standard, motilin. Additionally, Method B2 measures the actual signaling event, which makes it more relevant to the effect that is desired, whereas the assay of Method B3 simply measures GTP turnover.

TABLE 4

Demonstration of Antagonist Activity at the Motilin Receptor

	Aequorin (Method B2)[1]	
Compound	Binding (K_i)	IC_{50}
142	A	B
149	A	B
167	A	A
168	A	A
212	A	A
Motilin (human, porcine)[2]	0.6	not applicable

[1]Activity is listed as ranges with the following levels: A = 0.001-0.10 μM; B = 0.10-1.0 μM
[2]Human and porcine motilin are the same peptide.

In addition, a common and scientifically-accepted ex vivo assay for the measurement of agonist or antagonist activity at the motilin receptor is the contraction of rabbit duodenum or other gastrointestinal smooth muscle tissue.[A2-A4] Agonists are defined as compounds that induce >50% contraction relative to the motilin peptide, whereas antagonists are defined as compounds that cause >50% inhibition of the response to motilin. Compounds of the present invention have shown significant antagonist activity in this assay. For example, compound 144 exhibited a pA_2=6.95, while compound 165 had a pA_2=7.17, as calculated from the Schild plots of the response obtained at various concentrations as described in Method B4.

Gastric motility is generally measured in the clinical setting as the time required for gastric emptying and subsequent transit time through the GI tract. Gastric emptying scans are well known to those skilled in the art an, briefly, comprise use of an oral contrast agent, such as barium, or a radiolabeled meal. Solid and liquids can be measured independently. A test food or liquid is radiolabeled with an isotope (^{99m}Tc) and after ingestion or administration, transit time through the GI tract and gastric emptying are measured by visualization using gamma cameras. These studies are performed before and after the administration of the therapeutic agent to quantify the efficacy of the compound.

Example Method B1

Competitive Radioligand Binding Assay (Motilin Receptor)

Materials:

- Membranes were prepared from CHO cells stably transfected with the human motilin receptor and utilized at a quantity of 1.5 μg/assay point. [PerkinEimer™ SignalScreen® Product #6110544, PerkinElmer, Inc., Wellesley, Mass.]
- [^{125}]-Motilin (PerkinElmer, #NEX-378); final concentration: 0.04-0.06 nM Motilin (Bachem™, #H-4385, Bachem Bioscience Inc., King of Prussia, Pa.); final concentration: 1 μM
- Multiscreen® Harvest plates-GF/B (Millipore™, #MAHFB1H60, Billerica, Mass.)
- Deep-well polypropylene titer plate (Beckman Coulter™, #267006, Fullerton, Calif.)
- TopSeal-A™ (PerkinElmer, #6005185, Wellesley, Mass.)
- Bottom seal (Millipore™, #MATAH0P00, Billerica, Mass.)
- MicroScint-0™ (PerkinElmer, #6013611, Wellesley, Mass.)
- Binding Buffer: 50 mM Tris-HCl (pH 7.4), 10 mM $MgCl_2$, 1 mM EDTA, 0.1% BSA

Assay Volumes:

- 150 μL of membranes diluted in binding buffer
- 10 μL of compound diluted in binding buffer
- 10 μL of radioligand ([^{125}I]-Motilin) diluted in binding buffer

Final Test Concentrations (N=11) for Compounds:

10, 5, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.02, 0.01, 0.005 μM.

Compound Handling:

Compounds were provided frozen on dry ice at a stock concentration of 10 mM diluted in 100% DMSO and stored at −20° C. until the day of testing. On the test day, compounds were allowed to thaw at room temperature and than diluted in assay buffer according to the desired test concentrations. Under these conditions, the maximum final DMSO concentration in the assay was 0.5%.

Assay Protocol:

In deep-well plates, diluted cell membranes (1.5 μg/mL) are combined with 10 μL of either binding buffer (total binding, N=5), 1 μM motilin (non-specific binding, N=3) or the appropriate concentration of test compound. The reaction is initiated by addition of 10 μl of [^{125}I]-motilin (final conc. 0.04-0.06 nM) to each well. Plates are sealed with TopSeal-A, vortexed gently and incubated at room temperature for 2 hours. The reaction is arrested by filtering samples through pre-soaked (0.3% polyethyleneimine, 2 h) Multiscreen Harvest plates using a Tomtec® Harvester (Tomtec, Hamden, Conn.)), washed 9 times with 500 μL of cold 50 mM Tris-HCl (pH 7.4), and than plates are air-dried in a fumehood for 30 minutes. A bottom seal is applied to the plates prior to the addition of 25 μL of MicroScint-0™ to each well. Plates are then sealed with TopSeal-A® and counted for 30 sec per well on a TopCount® Microplate Scintillation and Luminescence Counter (PerkinElmer, Wellesley, Mass.) where results are expressed as counts per minute (cpm).

Data are analyzed by GraphPad™ Prism (GraphPad Software, San Diego, Calif.) using a variable slope non-linear regression analysis. K_i values were calculated using a K_d value of 0.16 nM for [^{125}I]-motilin (previously determined during membrane characterization).

$$D_{max} = 1 - \frac{\begin{array}{c}\text{test concentration with}\\ \text{maximal displacement}-\\ \text{non-specific binding}\end{array}}{\text{total binding} - \text{non-specific binding}} \times 100$$

where total and non-specific binding represent the cpm obtained in the absence or presence of 1 μM motilin, respectively.

Example Method B2

Aequorin Functional Assay (Motilin Receptor)

Materials:

- Membranes were prepared using AequoScreen™ (EUROSCREEN, Belgium) cell lines expressing the human motilin receptor (cell line ES-380-A; receptor accession #AF034632). This cell line is constructed by transfection of the human motilin receptor into CHO-K1 cells co-expressing $G_{\alpha 16}$ and the mitochondrially targeted Aequorin (Ref #ES-WT-A5).
- Motilin (Bachem™, #H-4385, Bachem Bioscience Inc., King of Prussia, Pa.)
- Assay buffer: DMEM-F12 (Dulbeccoe's Modified Eagles Medium) with 15 mM HEPES and 0.1% BSA (pH 7.0)
- Coelenterazine (Molecular Probes™, Leiden, The Netherlands)

Final Test Concentrations (N=5) for Compounds:

10, 3.16, 1, 0.316, 0.1 μM.

Compound Handling:

Compounds were provided as dry films at a quantity of approximately 1.2 μmol in pre-formatted 96-well plates. Compounds were dissolved in 100% DMSO at a concentration of 10 mM and stored at −20° C. until further use. Daughter plates were prepared at a concentration of 500 μM in 30% DMSO with 0.1% BSA and stored at −20° C. until testing. On the test day, compounds were allowed to thaw at room temperature and than diluted in assay buffer according to the desired test concentrations. Under these conditions, the maximum final DMSO concentration in the assay was 0.6%.

Cell Preparation:

Cells are collected from culture plates with Ca^{2+} and Mg^{2+}-free phosphate buffered saline (PBS) supplemented with 5 mM EDTA, pelleted for 2 minutes at 1000×g, resuspended in assay buffer (see above) at a density of 5×10^6 cells/mL and incubated overnight in the presence of 5 μM coelenterazine. After loading, cells were diluted with assay buffer to a concentration of 5×10^5 cells/mL.

Assay Protocol:

For agonist testing, 50 μl of the cell suspension was mixed with 50 μl of the appropriate concentration of test compound or motilin (reference agonist) in 96-well plates (duplicate samples). The emission of light resulting from receptor activation was recorded using the Functional Drug Screening System 6000 'FDSS 6000' (Hamamatsu Photonics K.K., Japan).

For antagonist testing, an approximate EC80 concentration of motilin (i.e. 0.5 nM; 100 μL) was injected onto the cell suspension containing the test compounds (duplicate samples) 15-30 minutes after the end of agonist testing and the consequent emission of light resulting from receptor activation was measured as described in the paragraph above.

Results are expressed as Relative Light Units (RLU). Concentration response curves were analyzed using GraphPad™ Prism® (GraphPad Software, San Diego, Calif.) by non-linear regression analysis (sigmoidal dose-response) based on the equation $E=E_{max}/(1+EC50/C)n$ where E is the measured RLU value at a given agonist concentration (C), E_{max} is the maximal response, EC_{50} is the concentration producing 50% stimulation and n is the slope index. For agonist testing, results for each concentration of test compound were expressed as percent activation relative to the signal induced by motilin at a concentration equal to the EC_{80} (i.e. 0.5 nM). For antagonist testing, results for each concentration of test compound were expressed as percent inhibition relative to the signal induced by motilin at a concentration equal to the EC_{80} (i.e. 0.5 nM).

Example Method B3

FlashPlate® Motilin [^{35}S]-GTPγS Functional Assay

Materials:

- Membranes were prepared from CHO cells stably transfected with the human motilin receptor and utilized at a quantity of 1.5 μg/assay point.

[PerkinElmer Signal/Screen® Product #6110544, PerkinElmer, Inc. Wellesley, Mass.]

- GTPγS Guanosine 5'-[γ-thio]triphosphate tetralithium salt (Sigma, #G-8634, Sigma-Aldrich, St. Louis, Mo.)
- [^{35}S]-GTPγS (PerkinElmer, #NEX-030H)
- Motilin (Bachem™, #H-4385, Bachem Bioscience Inc., King of Prussia, Pa.)
- 96-well FlashPlate® white polystyrene microplates (PerkinElmer, #SMP200, Wellesley, Mass.)
- Deep-well polypropylene titer plate (Beckman Coulter™, #267006, Fullerton, Calif.)
- TopSeal-A™ (PerkinElmer, #6005185, Wellesley, Mass.)
- Assay Buffer: 50 mM Tris (pH 7.4), 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 1 μM GDP, 0.1% BSA

Assay Volumes:

- 25 μL of compound diluted in assay buffer
- 25 μL of assay buffer (agonist assay) or 0.6 μM motilin (0.1 μM final concentration) diluted in assay buffer (antagonist assay)
- 100 μL of [^{35}S]-GTPγS diluted in assay buffer

Final Test Concentrations (N=12) for Compounds:

50, 20, 10, 5, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.02, 0.01 μM.

Compound Handling:

Compounds were provided frozen on dry ice at a stock concentration of 10 mM diluted in 100% DMSO and stored at −20° C. until the day of testing. On the test day, compounds were allowed to thaw at room temperature and than diluted in assay buffer according to the desired test concentrations. Under these conditions, the maximum final DMSO concentration in the assay was 0.5%.

Assay Protocol:

CHO membranes were immobilized into 96-well FlashPlate® microplates. Test compound, GTPγS, motilin and [^{35}S]-GTPγS were combined in each well according to the Assay Volumes described above.

For the assay to measure agonist activity, an additional 25 μl of buffer was added to each well in addition to 25 μL of either buffer (basal value, N=4), 1 μM (final conc.) motilin (E_{max} value, N=3), 25 μM (final conc.) GTPγS (non-specific value, N=4), or the appropriate concentration of test compound (N=3).

For the assay to measure antagonist activity, an additional 25 μL of either buffer (unstimulated control) or motilin (0.1 μM final conc.) is added to each well, in addition to either 25 μL of buffer (basal value, N=3), 1 μM (final conc.) motilin (E_{max} value, N=3), 25 μM (final conc.) GTPγS (non-specific value, N=4), or the appropriate concentration of test compound (N=3).

The reaction is initiated by addition of 100 mL of [^{35}S]-GTPγS to each well. Each plate is sealed (TopSeal-A™) and incubated in the dark at room temperature for 150 min. Then, plates are counted for 30 seconds per well on the TopCount® NXT.

Data were analyzed by GraphPad™ Prism® 3.0 (GraphPad Software, San Diego, Calif.) using non-linear regression analysis (sigmoidal dose-response) for the calculation of IC_{50}/EC_{50} values.

$$E_{max}(\text{agonist}) \text{ or } D_{max}(\text{antagonist}) = \frac{\text{Top} - \text{Bottom}}{\text{Bottom}} \times 100$$

Where Top and Bottom correspond to the top and bottom values of the dose-response curve calculated by GraphPad™ Prism®).

Example Method B4

Rabbit Duodenum Contractility Assay

Duodenal segments were vertically suspended in organ chambers of 10 mL filled with Krebs buffer and connected to an isotonic force transducer, with a preload of 1 g. After a stabilization period, the muscle strips were challenged with 10^{-4} M acetylcholine and washed. This was repeated until a stable maximal contraction was obtained (2-3 times), with an interval of at least 20 minutes.

After a stable base line was reached, test compounds were added to the bath. After 15 min incubation, a dose response to motilin was recorded by adding logarithmically increasing concentrations of motilin to the bath (final concentration 10^{-9} to 10^{-6} M). A blank experiment (no test compound present) was also performed. At the end of the dose response curve, a supramaximal dose of acetylcholine (10^{-4} M) was given and this response was used as a reference (100% contraction).

The results of experiments at different concentrations of test compound were combined and analyzed to derive the pA_2 value from the Schild plot.

It is appreciated that although specific experimental methods have been described herein for the purposes of illustration, various modifications to these experimental methods as well as alternate methods of experimentation may be used without departing from the scope of this invention.

TABLE 3

Binding activity of selected compounds

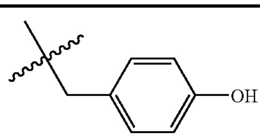
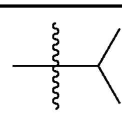
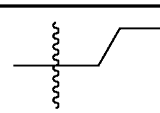
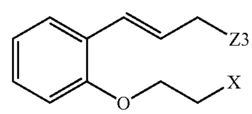
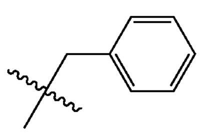
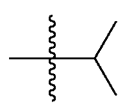
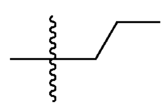
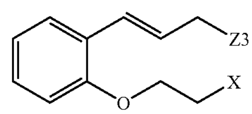
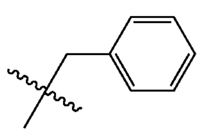
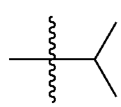
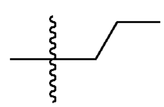
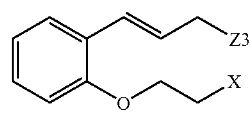
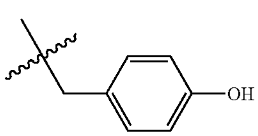
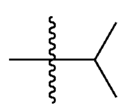
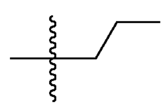
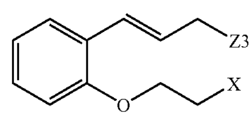
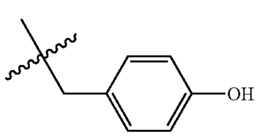
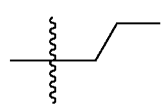
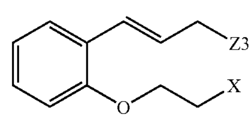
	R_1	R_3	R_6	T	K_i[1,2]
1					B
2					A
3					B
4					A
5		CH3			B

TABLE 3-continued

Binding activity of selected compounds

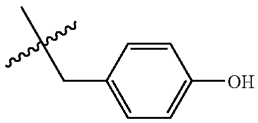
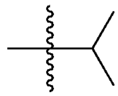
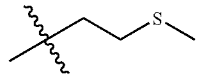
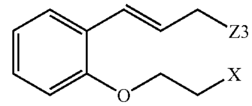
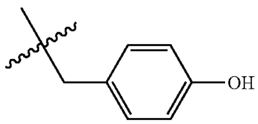
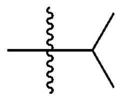
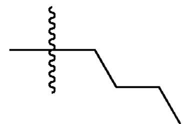
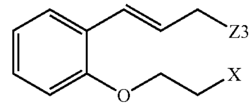
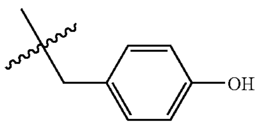
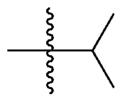
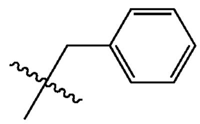
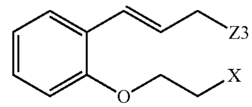
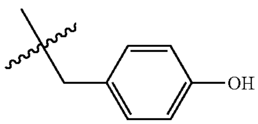
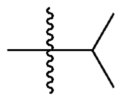
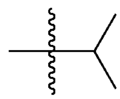
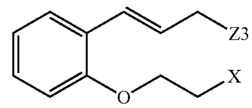
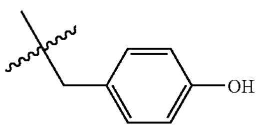
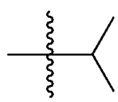
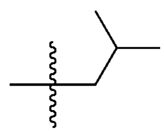
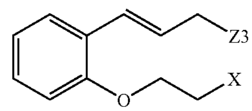
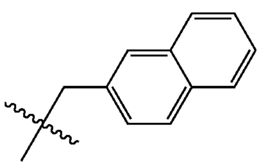
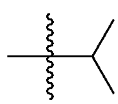
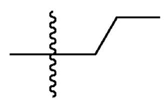
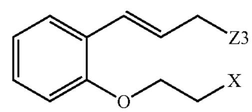
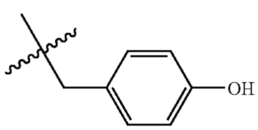
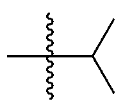
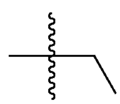
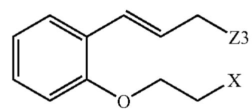
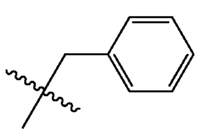
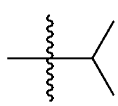
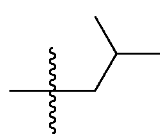
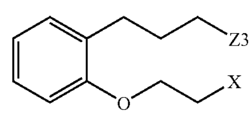
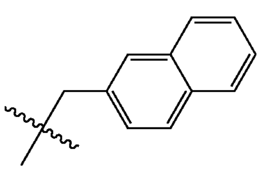
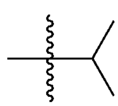
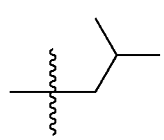
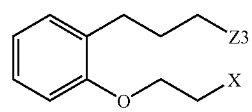
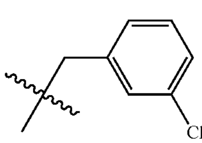
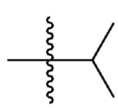
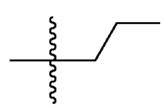
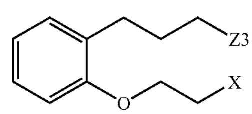
	R_1	R_3	R_6	T	K_i[1,2]
6					B
7					B
8					B
9					B
10					A
11					A
12					B
13					B
14					B
15					A

TABLE 3-continued

Binding activity of selected compounds

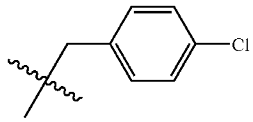
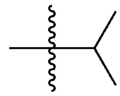
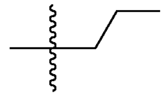
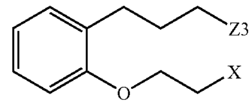
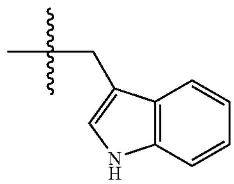
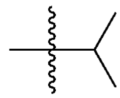
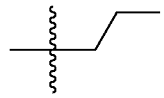
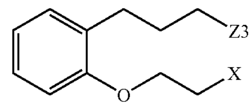
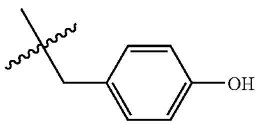
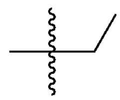
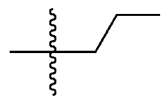
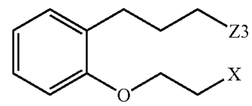
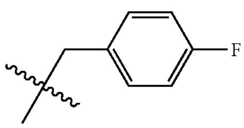
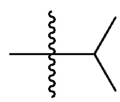
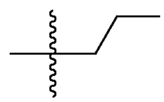
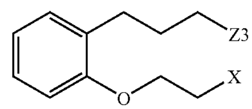
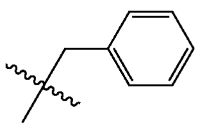
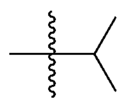
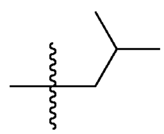
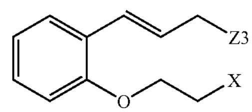
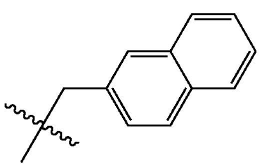
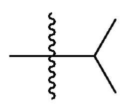
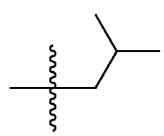
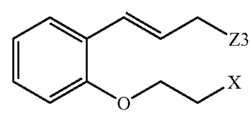
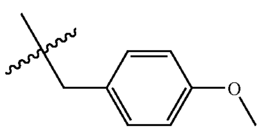
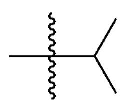
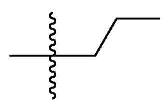
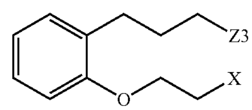
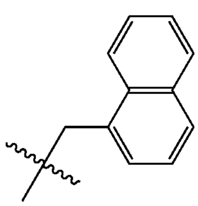
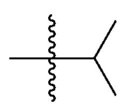
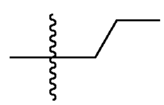
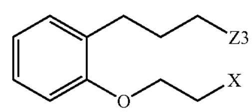
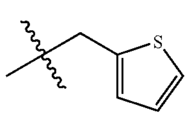
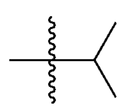
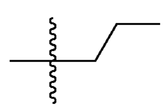
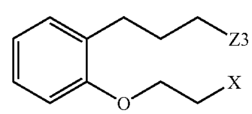
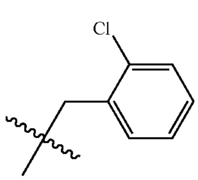
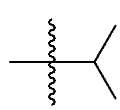
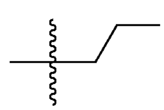
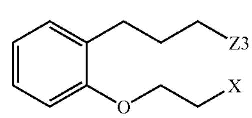
	R_1	R_3	R_6	T	K_i[1,2]
16					A
17					B
18					B
19					A
20					B
21					A
22					A
23					A
24					A
25					B

TABLE 3-continued

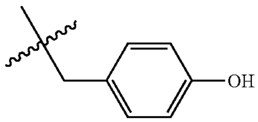
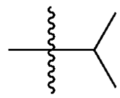
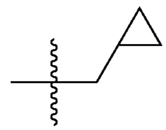
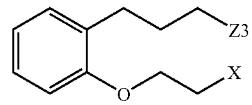
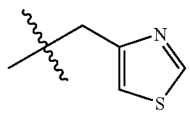
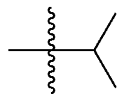
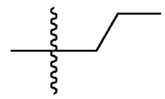
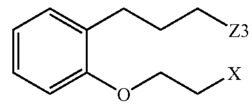
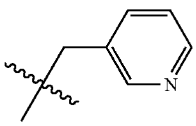
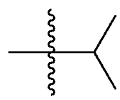
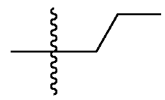
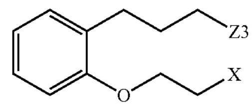
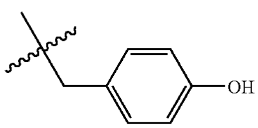
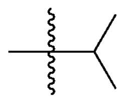
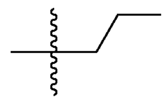
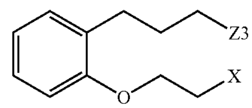
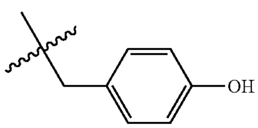
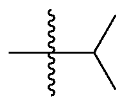
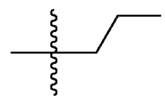
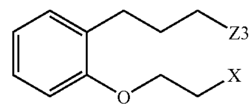
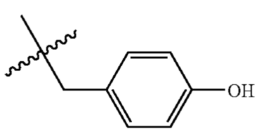
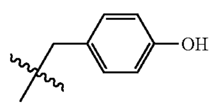
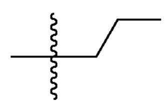
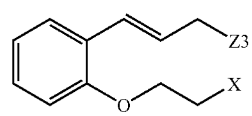
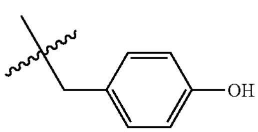
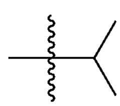
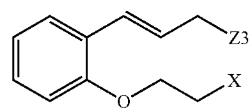
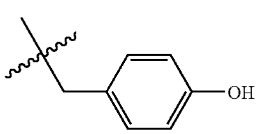
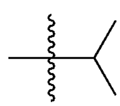
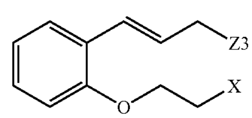
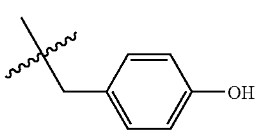
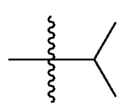
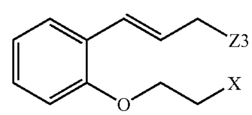
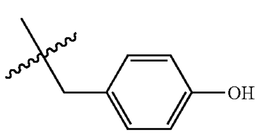
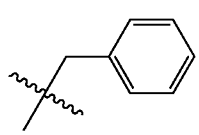
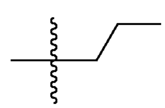
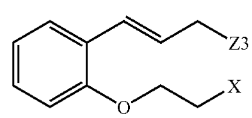
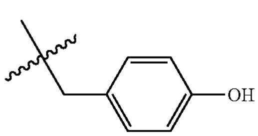
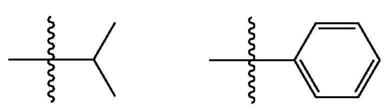
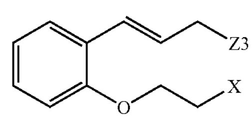
Binding activity of selected compounds					
	R_1	R_3	R_6	T	K_i[1,2]
26					A
27					B
28					B
29					B
30					B
34					B
38			CH_3		C
39			H		B
40			H		C
41					C
52					B

TABLE 3-continued

Binding activity of selected compounds

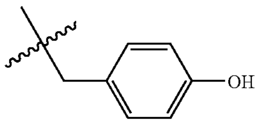
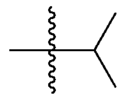
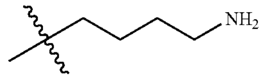
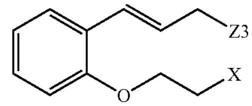
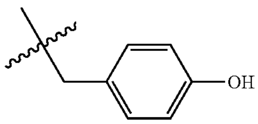
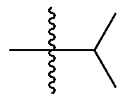
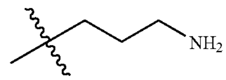
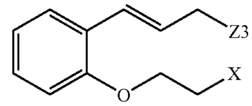
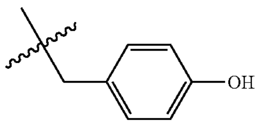
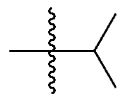
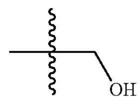
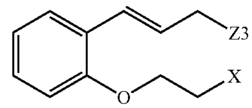
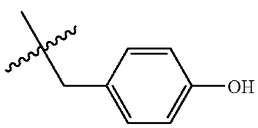
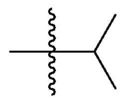
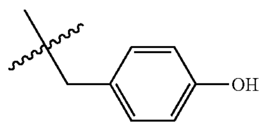
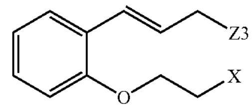
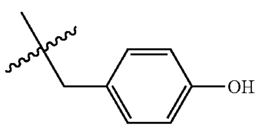
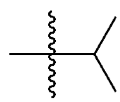
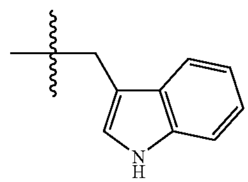
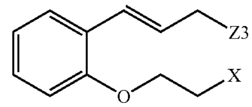
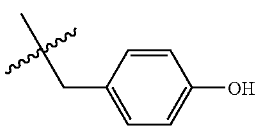
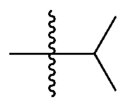
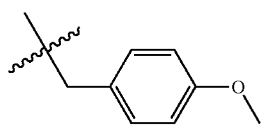
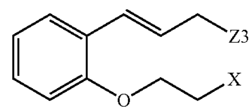
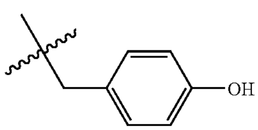
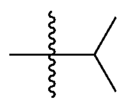
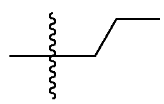
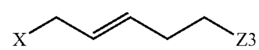
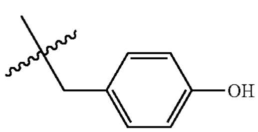
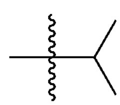
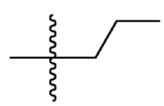
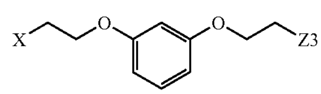
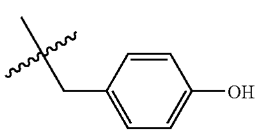
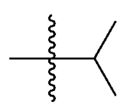
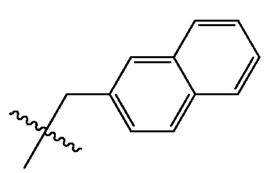
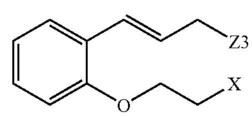
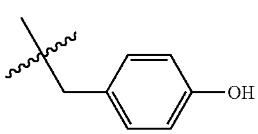
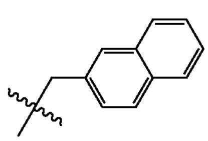
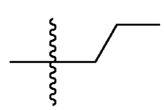
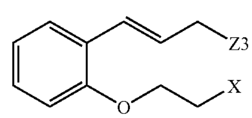
	R_1	R_3	R_6	T	$K_i^{1,2}$
55					B
56					B
57					B
58					B
59					B
60					C
65					B
71					B
72					B
76					C

TABLE 3-continued

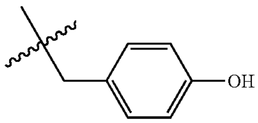
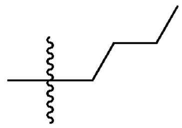
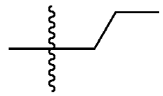
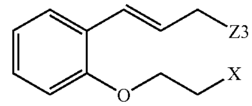
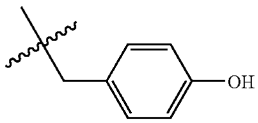
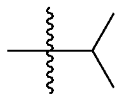
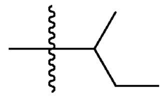
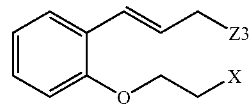
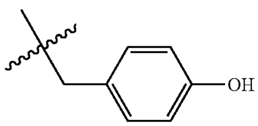
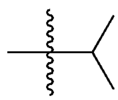
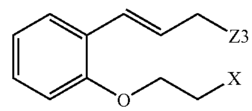
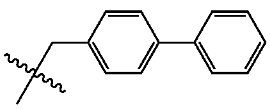
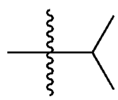
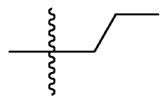
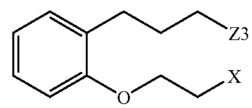
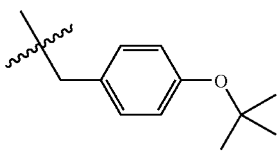
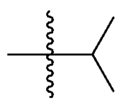
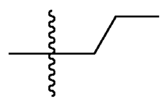
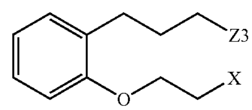
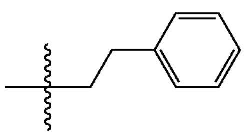
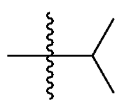
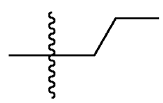
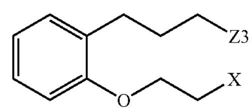
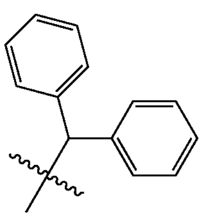
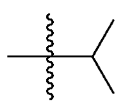
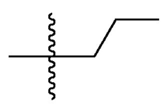
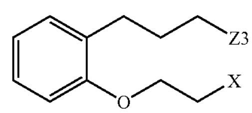
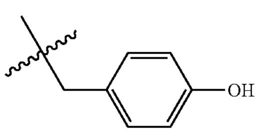
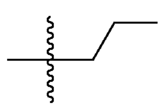
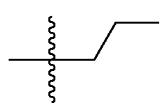
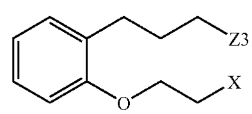
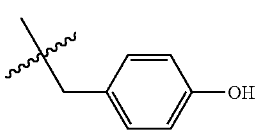
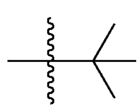
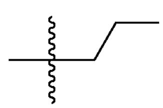
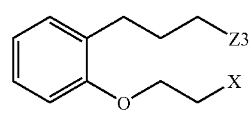
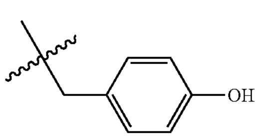
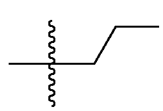
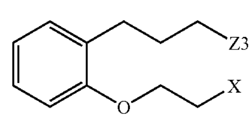
Binding activity of selected compounds					
	R_1	R_3	R_6	T	K_i[1,2]
77					C
80					B
85			H		B
87					B
88					C
89					C
90					C
91					C
92					B
96		H			C

TABLE 3-continued

Binding activity of selected compounds

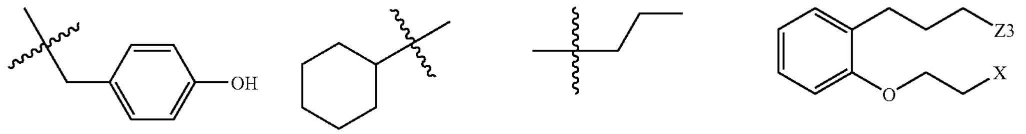
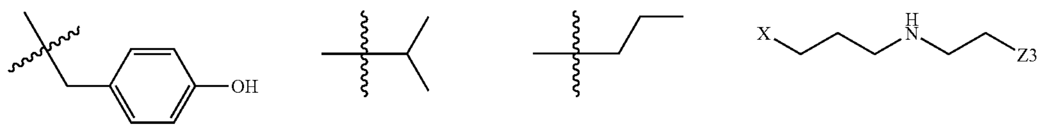
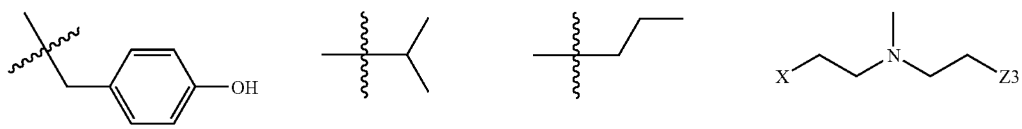
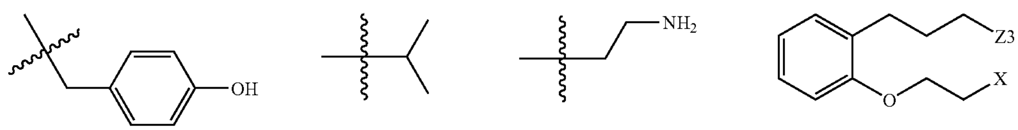
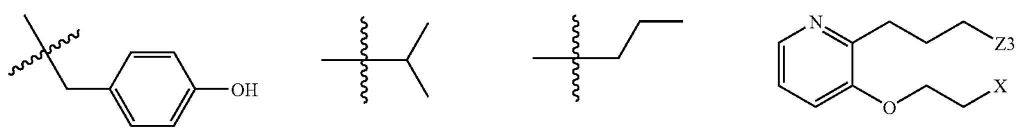
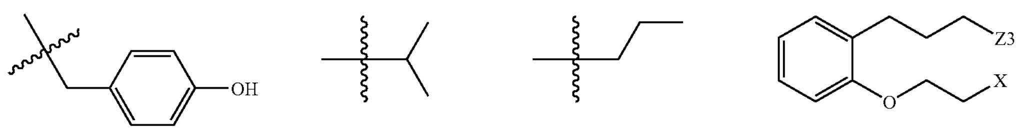
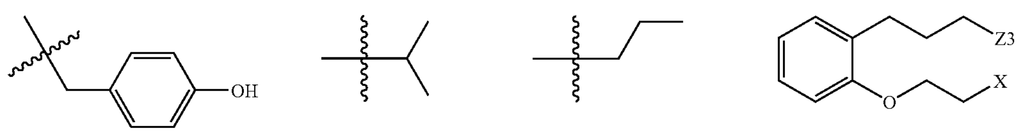
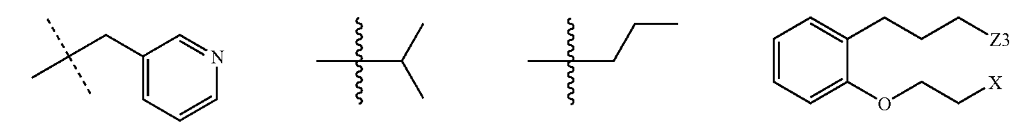
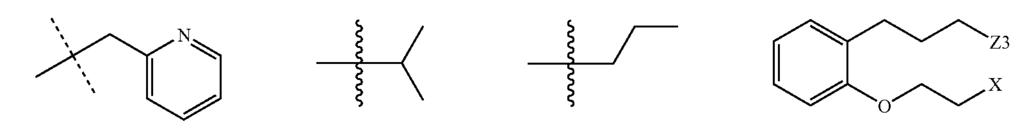
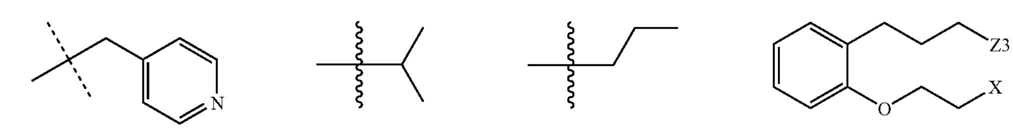
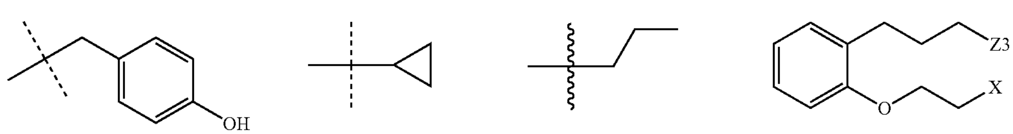
	R1 / R3 / R6 / T	K_i[1,2]
97		C
98		C
99		C
109		B
110		B
111		B
112		B
122		B
123		B
124		B
125		B

TABLE 3-continued

Binding activity of selected compounds

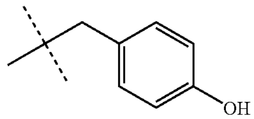
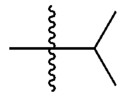
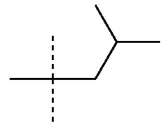
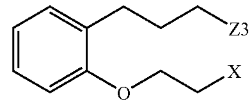
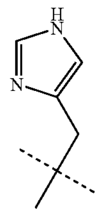
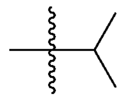
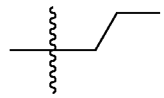
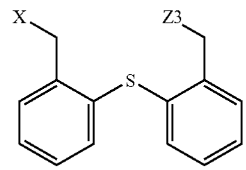
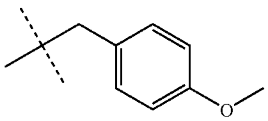
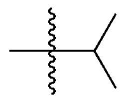
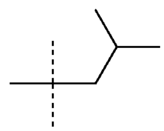
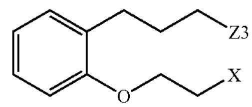
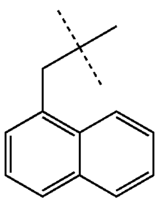
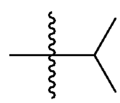
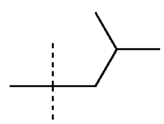
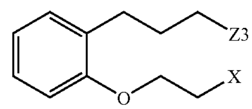
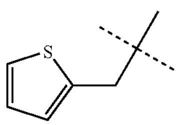
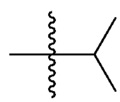
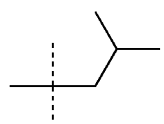
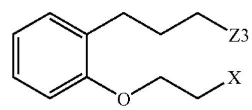
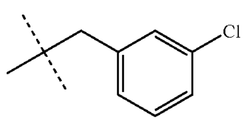
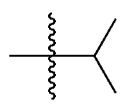
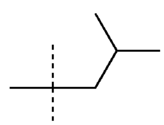
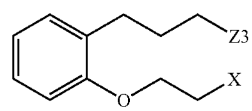
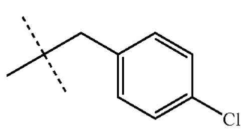
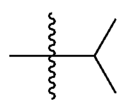
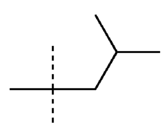
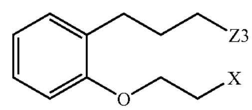
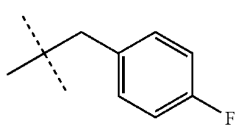
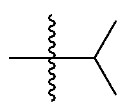
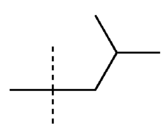
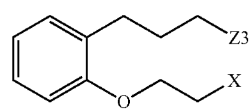
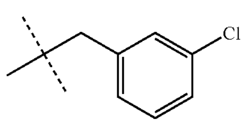
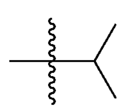
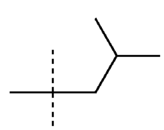
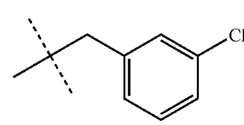
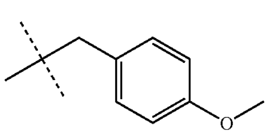
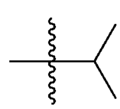
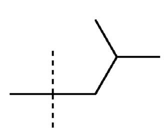
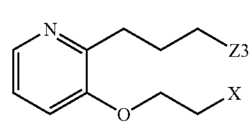
	R_1	R_3	R_6	T	K_i[1,2]
126					B
127					B
128					B
129					A
130					B
131					A
132					A
133					A
134					C
135					B

TABLE 3-continued

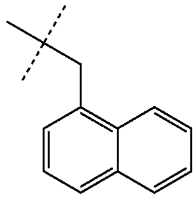
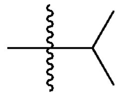
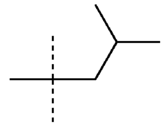
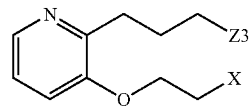
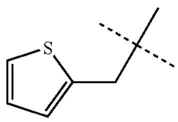
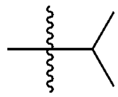
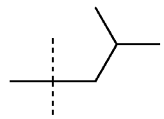
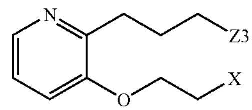
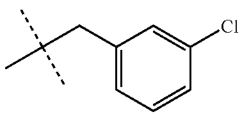
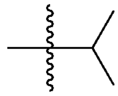
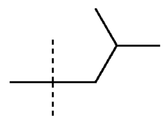
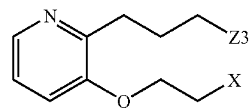
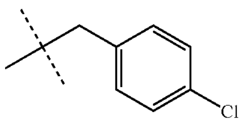
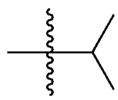
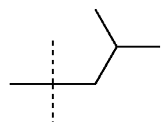
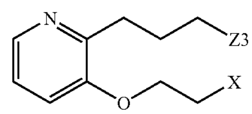
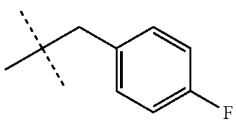
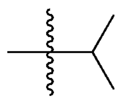
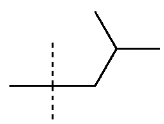
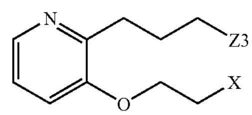
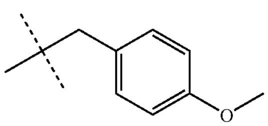
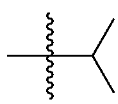
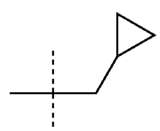
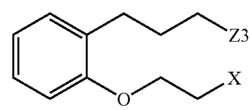
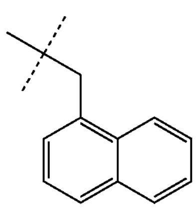
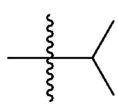
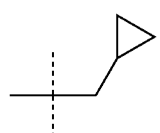
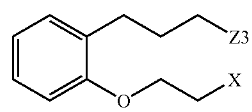
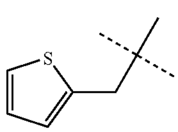
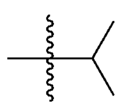
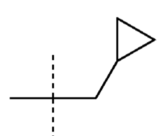
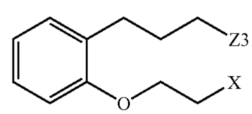
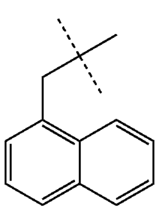
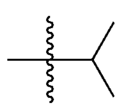
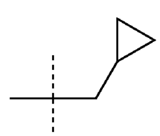
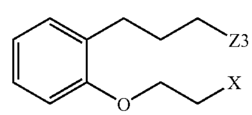
Binding activity of selected compounds					
	R_1	R_3	R_6	T	K_i[1,2]
136					B
137					B
138					B
139					B
140					B
141					A
142					A
143					B
144					A

TABLE 3-continued

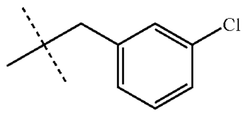
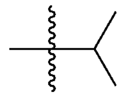
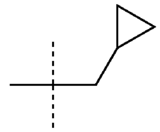
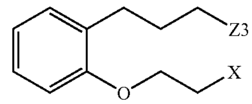
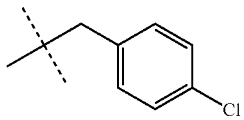
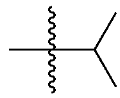
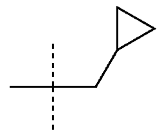
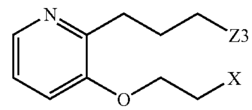
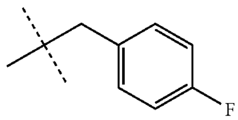
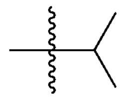
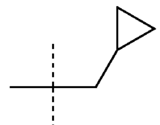
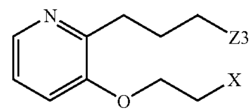
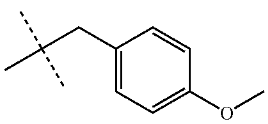
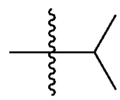
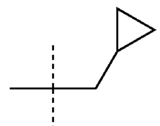
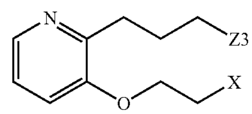
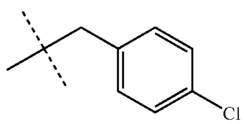
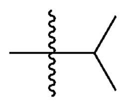
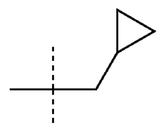
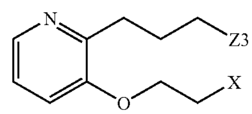
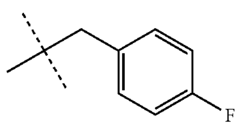
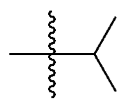
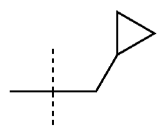
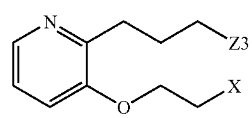
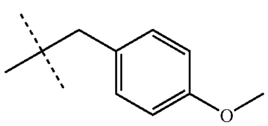
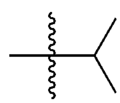
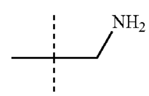
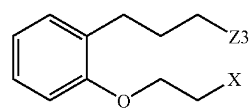
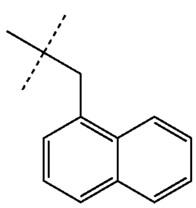
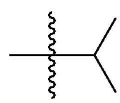
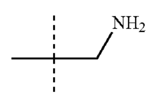
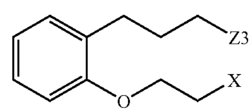
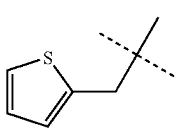
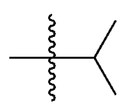
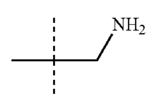
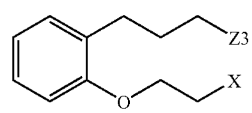
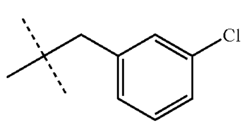
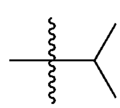
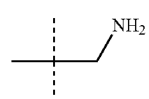
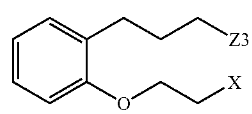
Binding activity of selected compounds					
	R_1	R_3	R_6	T	$K_i^{1,2}$
146					A
147					B
148					B
149					A
150					B
151					B
152					B
153					B
154					B
155					A

TABLE 3-continued

Binding activity of selected compounds

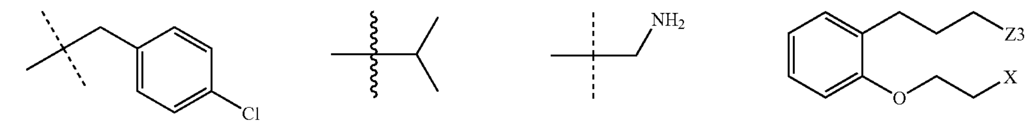
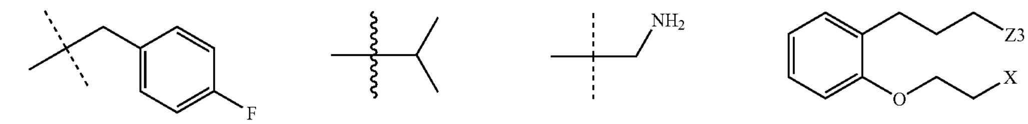
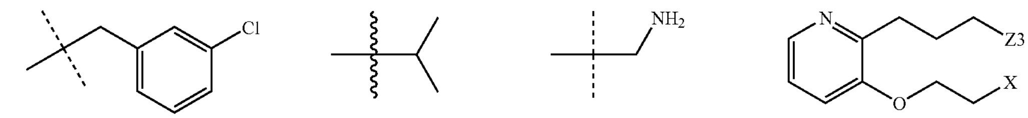
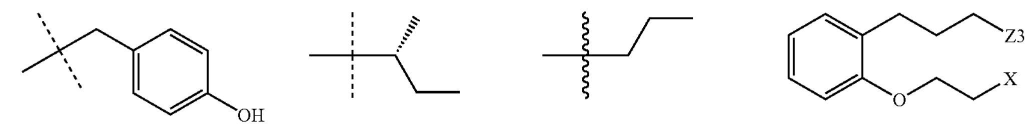
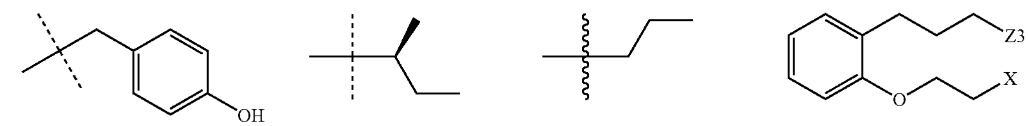
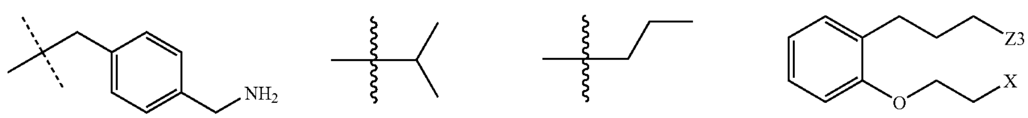
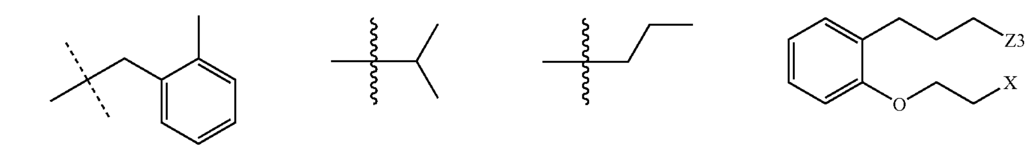
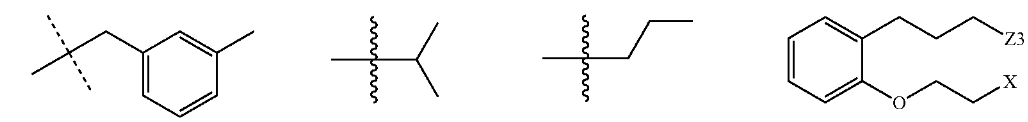
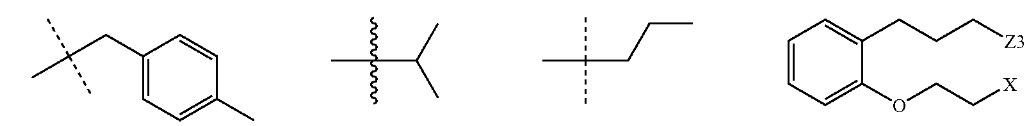
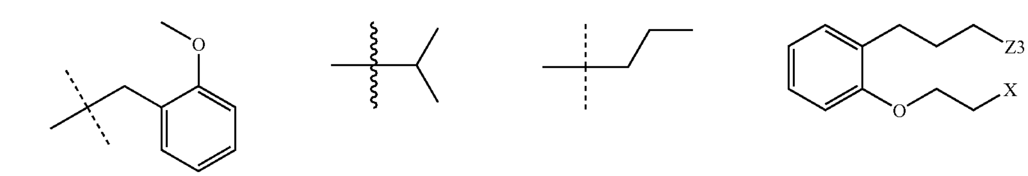
	R_1	R_3	R_6	T	$K_i^{1,2}$
156					A
157					B
158					A
159					B
160					B
161					B
162					B
163					A
164					B
165					A
166					B

TABLE 3-continued

Binding activity of selected compounds

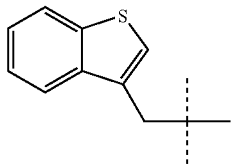
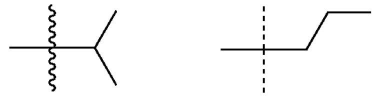
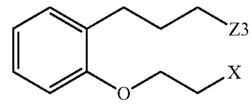
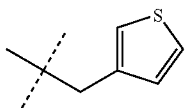
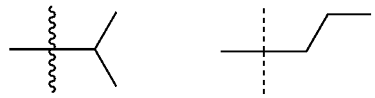
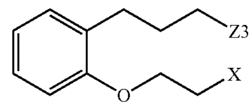
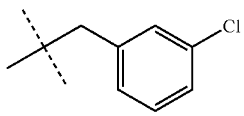
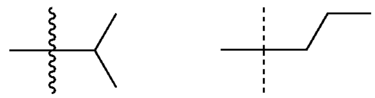
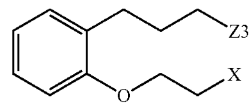
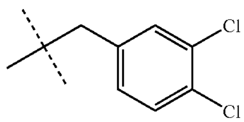
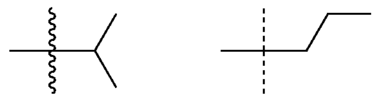
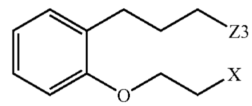
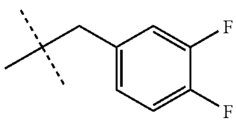
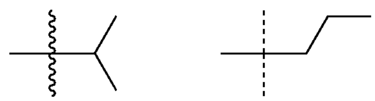
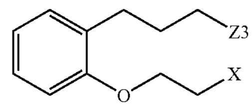
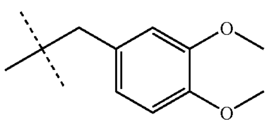
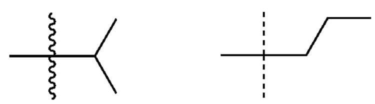
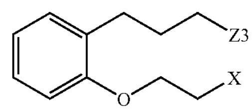
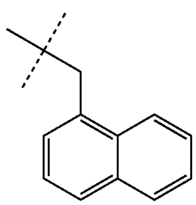
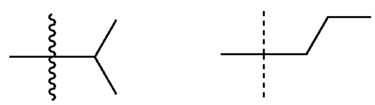
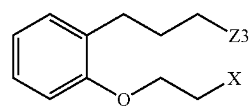
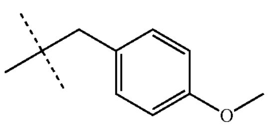
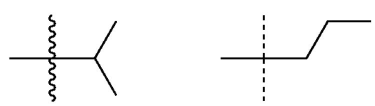
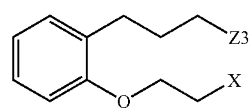
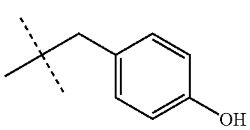
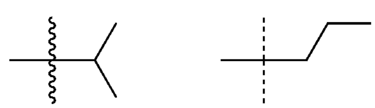
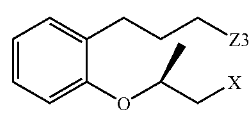
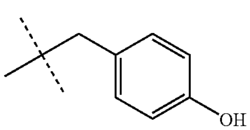
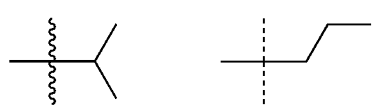
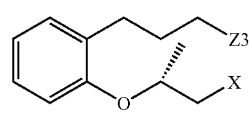
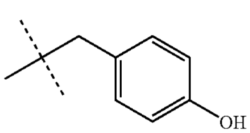
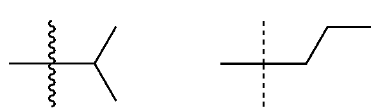
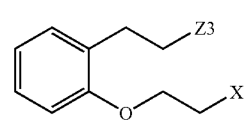
	R_1	R_3	R_6	T	K_i[1,2]
167					A
168					A
169					B
170					A
171					A
172					A
173					B
174					B
175					B
176					B
177					B

TABLE 3-continued

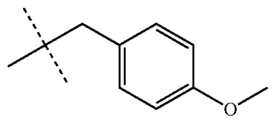
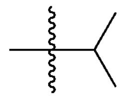
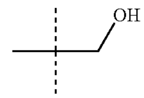
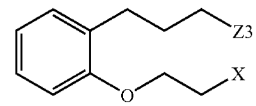
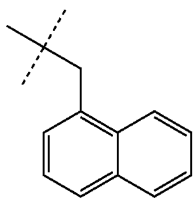
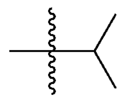
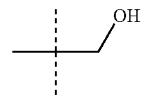
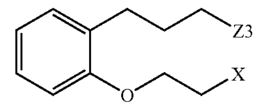
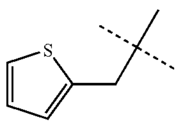
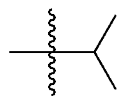
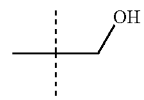
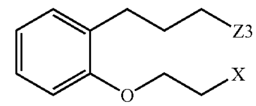
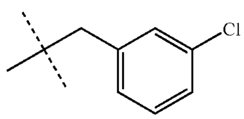
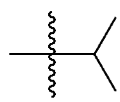
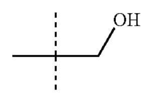
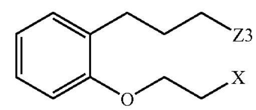
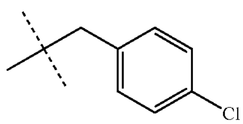
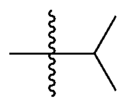
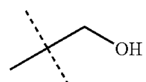
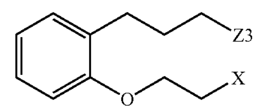
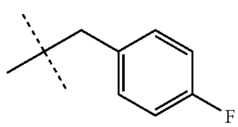
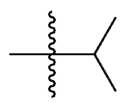
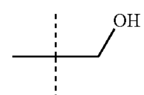
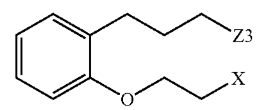
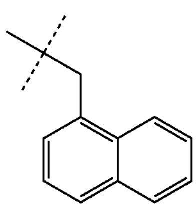
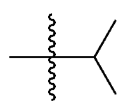
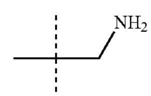
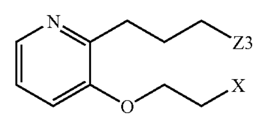
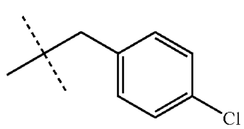
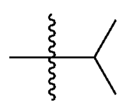
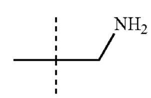
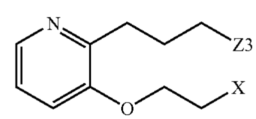
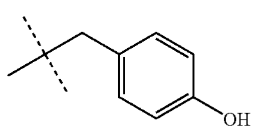
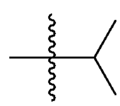
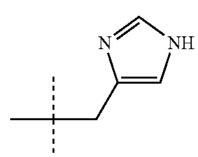
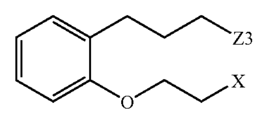
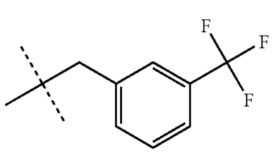
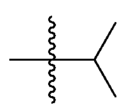
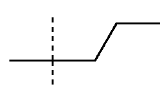
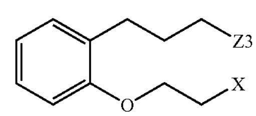
Binding activity of selected compounds					
	R_1	R_3	R_6	T	K_i[1,2]
178					B
179					B
180					B
181					A
182					A
183					B
184					B
185					B
186					B
187					A

TABLE 3-continued

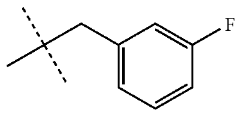
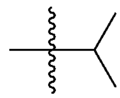
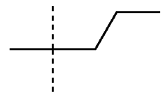
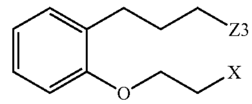
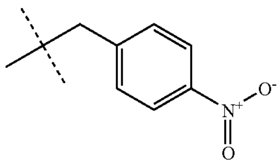
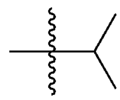
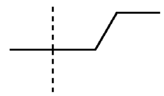
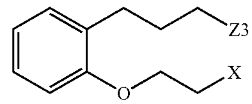
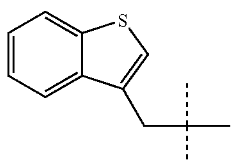
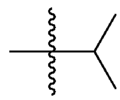
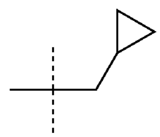
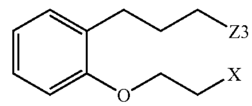
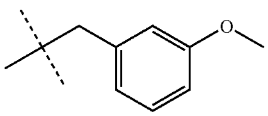
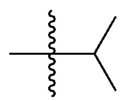
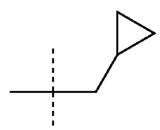
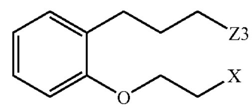
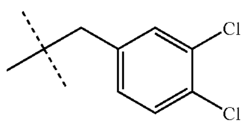
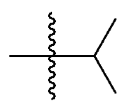
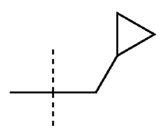
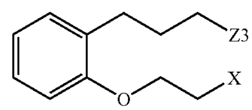
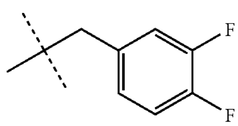
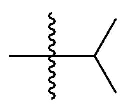
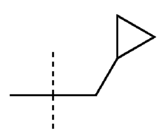
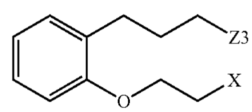
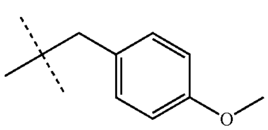
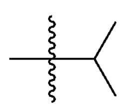
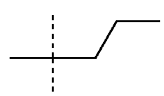
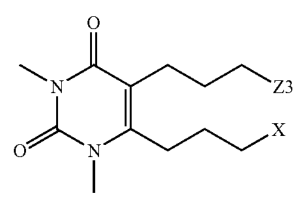
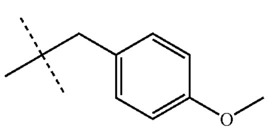
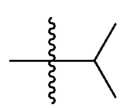
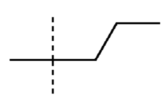
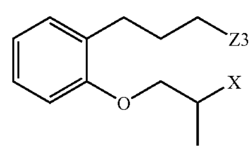
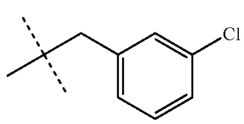
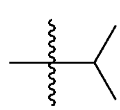
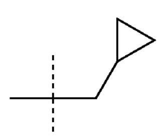
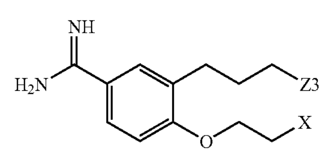
Binding activity of selected compounds					
	R_1	R_3	R_6	T	$K_i^{1,2}$
188					A
189					B
190					A
191					A
192					A
193					A
194					B
195					A
196					

TABLE 3-continued

Binding activity of selected compounds

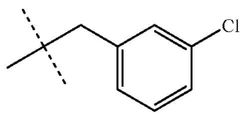
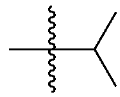
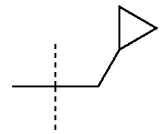
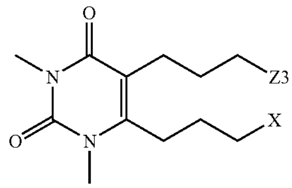
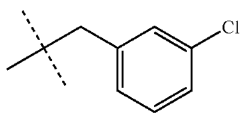
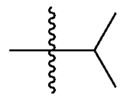
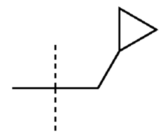
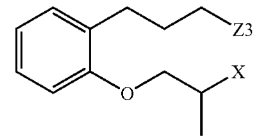
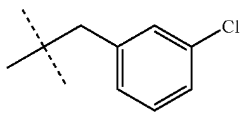
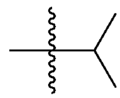
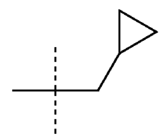
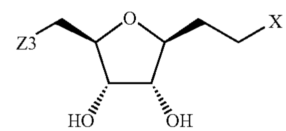
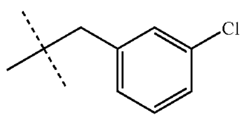
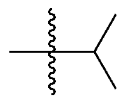
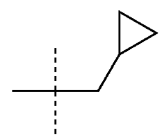
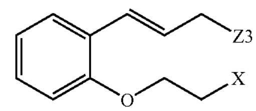
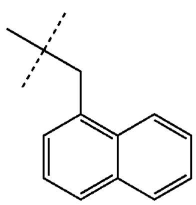
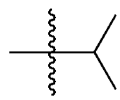
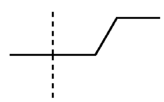
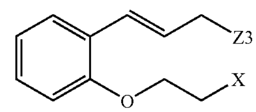
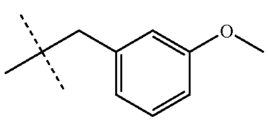
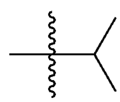
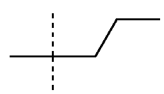
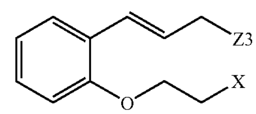
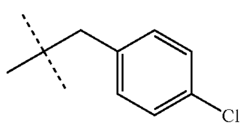
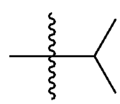
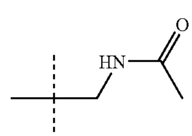
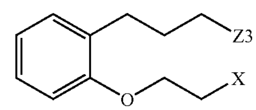
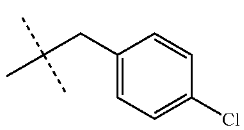
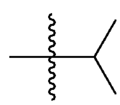
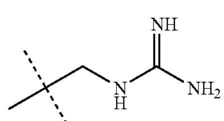
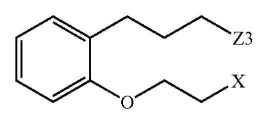
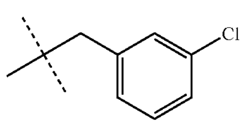
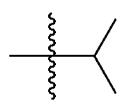
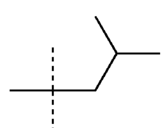
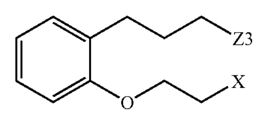
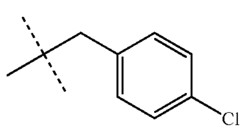
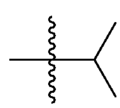
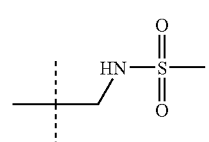
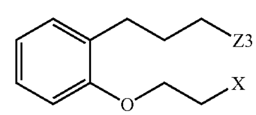
	R_1	R_3	R_6	T	$K_i^{1,2}$
197					
198					A
199					B
200					A
201					B
202					A
203					B
204					A
205					B
206					B

TABLE 3-continued

Binding activity of selected compounds

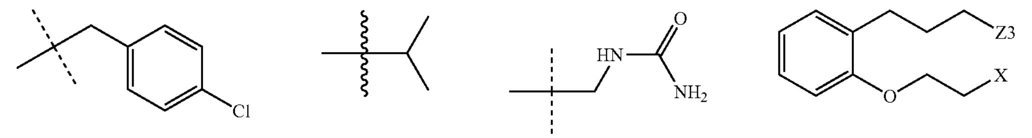
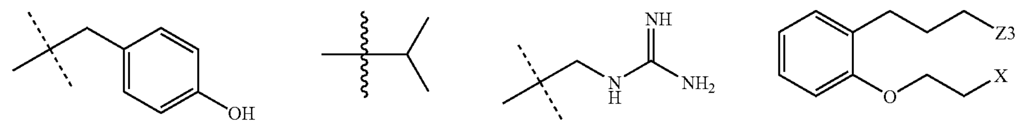
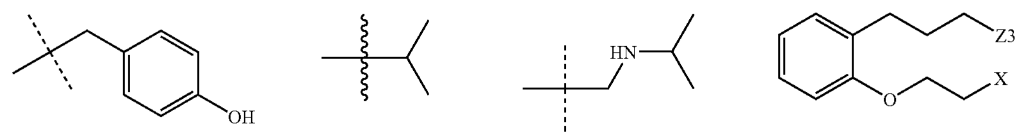
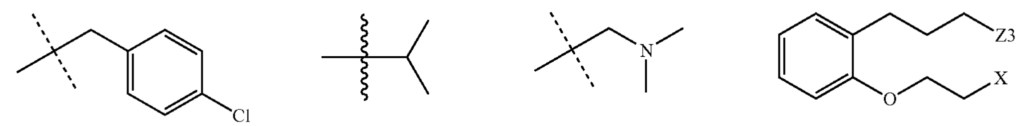
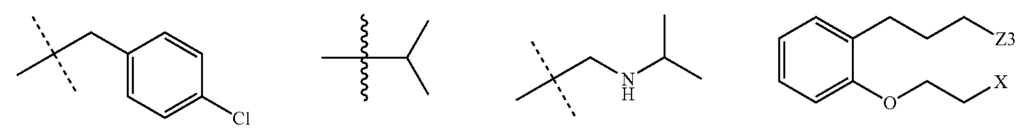
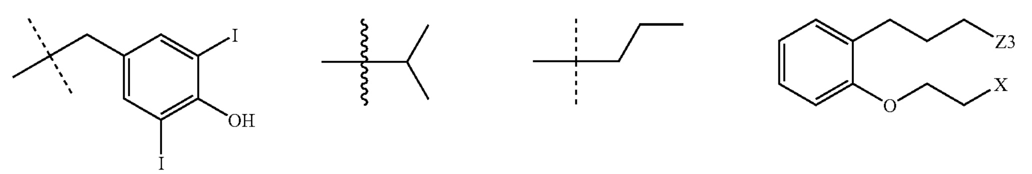
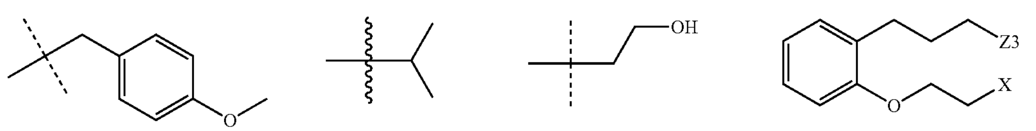
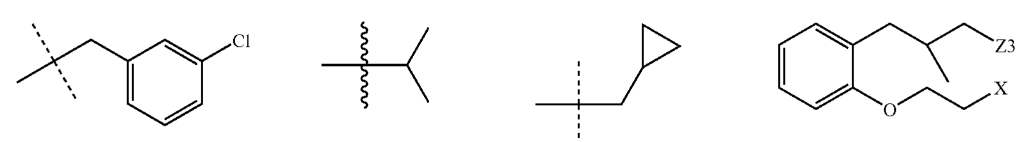
	R_1 — R_3 — R_6 — T	K_i[1,2]
207		B
208		B
209		C
210		
211		A
212		A
213		B
214		B
215		B
216		A
217		B

TABLE 3-continued

Binding activity of selected compounds

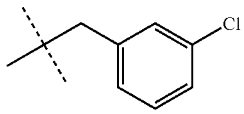
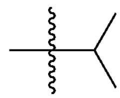
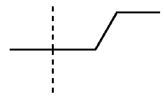
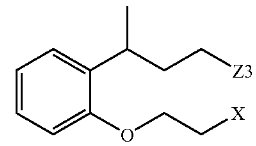
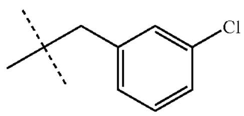
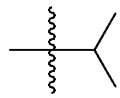
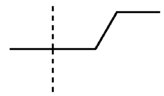
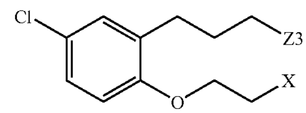
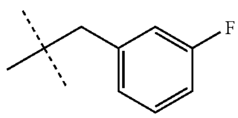
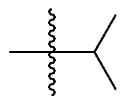
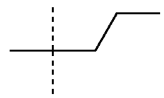
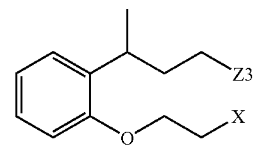
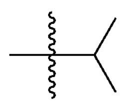
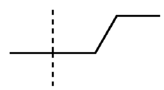
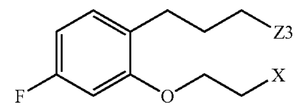
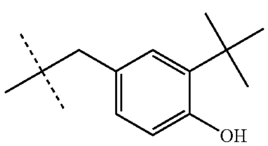
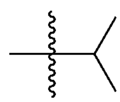
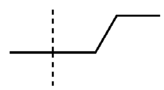
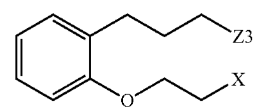
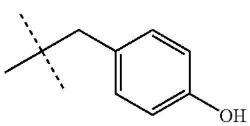
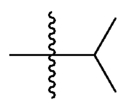
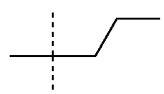
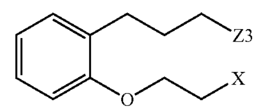
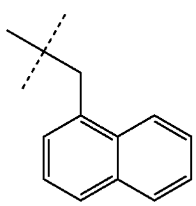
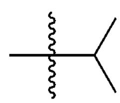
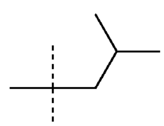
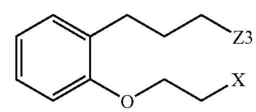
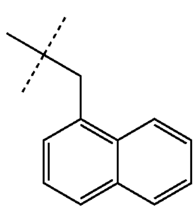
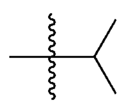
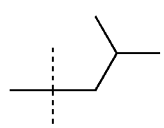
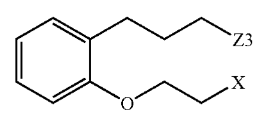
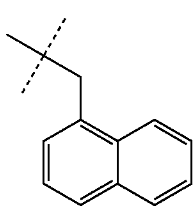
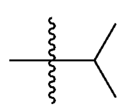
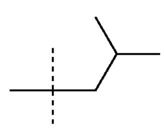
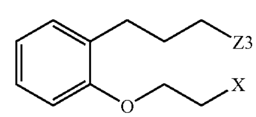
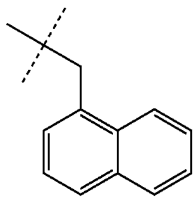
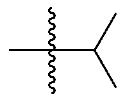
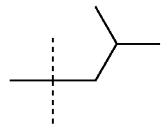
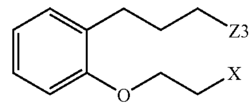
	R_1	R_3	R_6	T	K_i[1,2]
218					A
219					B
220					A
221					B
222					A
223					C
224					B
225					B
226					C

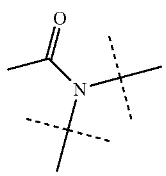
TABLE 3-continued

Binding activity of selected compounds					
	R_1	R_3	R_6	T	K_i[1,2]
227					B

Notes
Radioligand competitive binding assays performed using Method B1
Values reported as ranges: A = 0.001-0.100 μM; B = 0.100-1.0 μM; C = 1.0-10.0 μM

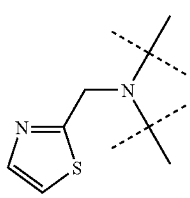
X is NH except for:

Compound 223 and 225, X is:

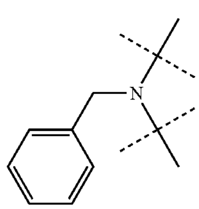


Compound 224, X is NMe

Compound 226, X is:

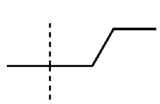


Compound 227, X is



Z_1, Z_2 and Z_3 are NH except for compounds 30, 173 and 174 and where Z_1 is O and compound III where Z_2 is O.

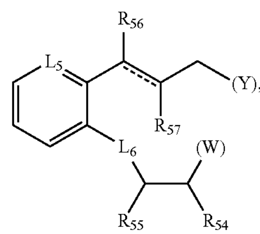
R_2, R_4 and R_5 are hydrogen except for compound 85 where it is:



m, n_1 and p are zero.

What is claimed is:

1. A compound of formula W-T-Y, wherein W and Y are independently selected from the group consisting of —OH, —NH_2 and —NHR_{60}, wherein R_{60} is lower alkyl, and T is the following structure:



wherein

L_5 is CH or N;

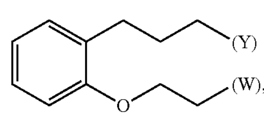
L_6 is $CR_{52}R_{53}$ or O, wherein R_{52} and R_{53} are independently selected from the group consisting of hydrogen and lower alkyl;

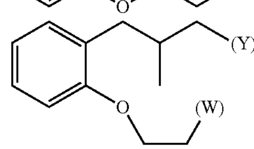
R_{54} and R_{55} are independently lower alkyl; and, when L_6 is $CR_{52}R_{53}$, R_{55} is also selected from hydroxy;

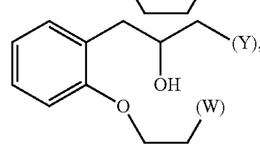
R_{56} is hydrogen or lower alkyl, and R_{57} is selected from the group consisting of hydrogen and lower alkyl, and, when no double bond is present between the carbon atoms to which R_{56} and R_{57} are bonded, R_{56} and R_{57} are also independently selected from hydroxy; and

(W) indicates the point of attachment of T to W; and (Y) indicates the point of attachment of T to Y;

with the proviso that T is not the following:

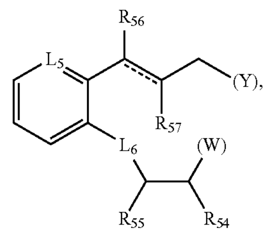


 or



further comprising one or more protecting groups.

2. A compound of formula W-T-Y, wherein W and Y are independently selected from the group consisting of —OH, —NH_2 and —NHR_{60}, wherein R_{60} is lower alkyl, and T is the following structure:



wherein

L_5 is CH or N;

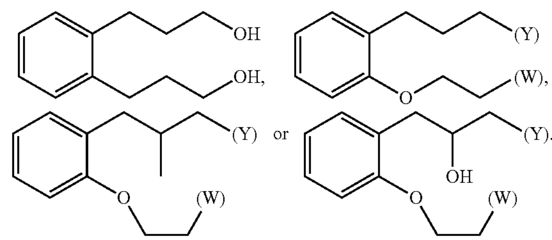
L_6 is $CR_{52}R_{53}$ or O, wherein R_{52} and R_{53} are independently selected from the group consisting of hydrogen and lower alkyl;

R_{54} and R_{55} is lower alkyl; and, when L_6 is $CR_{52}R_{53}$, R_{55} is also selected from hydroxy;

R_{56} and R_{57} are independently selected from the group consisting of hydrogen and lower alkyl, and, when no double bond is present between the carbon atoms to which R_{56} and R_{57} are bonded, R_{56} and R_{57} are also independently selected from hydroxy; and

(W) indicates the point of attachment of T to W; and (Y) indicates the point of attachment of T to Y;

with the proviso that T is not the following:



3. The compound of claim 2, further comprising one or more protecting groups.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

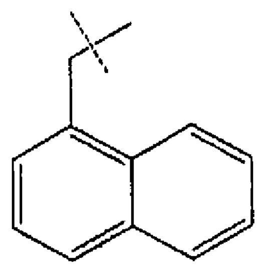
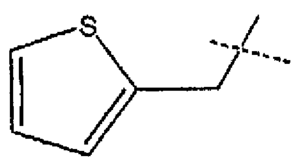
PATENT NO. : 9,181,298 B2
APPLICATION NO. : 12/273638
DATED : November 10, 2015
INVENTOR(S) : Marsault et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the specification

Column 4, Line 2: Please correct "(=O-O," to read -- (=O)-, --

Column 71, Compounds 143 and 144: Please correct the first compound on each row to read as follows:

143	
144	

Signed and Sealed this
Fifteenth Day of November, 2016

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office